

Chirality Transfer in Electrophilic Reactions of Hydrovinylation Adducts

A Senior Honors Thesis

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by

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Abstract

As a result of new regulatory requirements and a deeper understanding of the role of chirality in biological systems, the modern pharmaceutical industry has become dependent on chemical processes which can selectively produce enantiopure compounds without wasteful resolutions. The asymmetric hydrovinylation reaction has been demonstrated to yield a number of popular NSAIDs with exceptionally high selectivity. The major thrust of this project was to examine how well chirality could be transferred from an asymmetric center installed by the hydrovinylation to a new chiral center formed with an achiral electrophilic reagent. The highest levels of selectivity were observed for dihydroxylation and oxymercuration reactions, both of which employed sterically demanding third row transition metal reagents. In addition to investigating selectivity, the photochemical Barton reaction was examined as a route to functionalize methyl groups that result from the hydrovinlation of terminal olefins. Preliminary scouting experiments suggest the Barton reaction may provide a viable route to functionalization.

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1 Introduction

1.1 The Importance of Chirality

Chirality is a chemical phenomenon that arises when mirror images of a molecule are not super imposable upon each other. The two mirror images, referred to as enantiomers, have the same constitution and nearly the same physical properties; however, they may be recognized as unique compounds in environments containing other chiral molecules. In certain cases mixtures of enantiomers may have slightly different physical properties from the pure compounds and pairs of enantiomers will rotate plane polarized light differently. Biological environments are constructed from chiral molecules and are therefore able to distinguish between enantiomers. The human nose is lined with chiral receptors, and as a simple example the molecule (R)-limonene has a pleasant citrus odor, whereas its enantiomer smells strongly of turpentine. In a more serious example, one enantiomer of the popular sedative drug thalidomide was shown to be teratogenic while the other had the desired therapeutic effect.¹ Shortcomings in regulatory requirements and a lack of understanding of developmental physiology and chirality led to an estimated 40,000 cases of nerve damage and 8,000-12,000 disfigured infants, roughly 5,000 of which survived beyond childhood.² Although thalidomide cannot be marketed as a single enantiomer because it rapidly converts to an equivalent mixture of enantiomers, or racemic mixture, under physiological conditions the tragedy ultimately led to more stringent regulations.³ In 1992 the United States Food and Drug Administration (FDA) revised their policy on chiral drugs, stating that each enantiomer of newly produced drugs would need to be characterized if the product were to be marketed as a racemic mixture.⁴

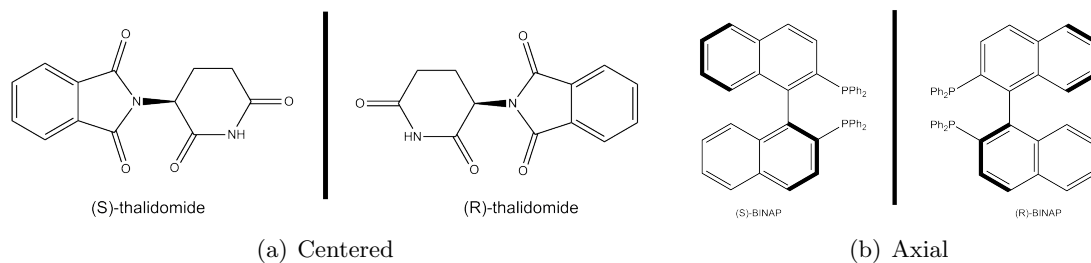


Figure 1: Two Common Forms of Chirality in Organic Molecules

Chirality in organic molecules most commonly arises from carbon's propensity to form four bonds. When the four bonds are unique and in the absence of symmetry, two non-super imposable mirror images are formed. This form of centered chirality is present in thalidomide, shown above in

figure 1a. Chirality may also arise in systems that contain a hindered rotational axis. Axially chiral 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) is an important compounds used as a ligand for asymmetric hydrogenation of olefins and 1,3-hydrogen shifts.⁵ The BINAP ligand is pictured above in Figure 1b. As a result of new FDA policies, the modern pharmaceutical industry has become dependent on chemical processes that can selectively produce molecules containing both centered and axial forms of chirality. In 1985 more than 75% of chiral drugs were marketed as racemic mixtures.⁶ By 1999 chiral drugs marketed as a single enantiomer accounted for 32% of pharmaceutical sales.⁷ In 2006 75% of new drugs approved by the FDA were to be sold as single enantiomers.⁸ Only 5% of the approved drugs were racemic mixtures and the remaining 20% were achiral.

1.2 The Asymmetric Hydrovinylation Reaction

The hydrovinylation reaction is a chemical transformation in which ethylene is added across a double bond as hydrogen and a vinyl group. Both branched and linear products can form, however in order to produce a new chiral center the branched product must form.⁹ The first large scale asymmetric hydrovinylation reaction of styrene was mentioned by Wilke and co-workers in 1988, however the details of the reaction were unpublished.¹⁰ The reaction utilized a nickel(II) salt with a complicated ligand and required a Lewis acid which severely limited functional group compatibility. Further development of the reaction was met with additional challenges. Oligomerization of starting material and isomerization of desired branched olefins to more stable conjugated systems limited the viability of the reaction.

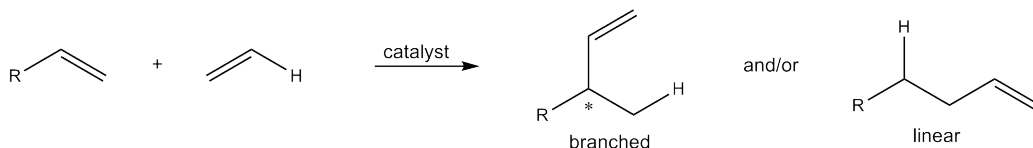


Figure 2: The Hydrovinylation Reaction

In 1998 RajanBabu and co-workers reported a new protocol for the hydrovinylation reaction that replaced Wilke's Lewis acid and introduced a weakly coordinating counteranion.¹¹ The new reaction conditions facilitated the regioselective hydrovinylation of vinyl arenes bearing a variety of functional groups incompatible with the Wilke conditions. When the reaction was carried out

at -56°C using 0.7 mol% of catalyst, no oligomerization of the starting material or of ethylene was found. The ligand used for these reactions was achiral triphenylphosphine; therefore, the reaction produced a racemic mixture. The new conditions were, however, easily amenable to the use of chiral phosphine ligands which could be tuned to provide the maximum level of enantioselectivity. The Leitner group soon followed with a report of excellent enantioselectivities for a number of substrates by utilizing tunable chiral phosphoramidite ligands.¹²

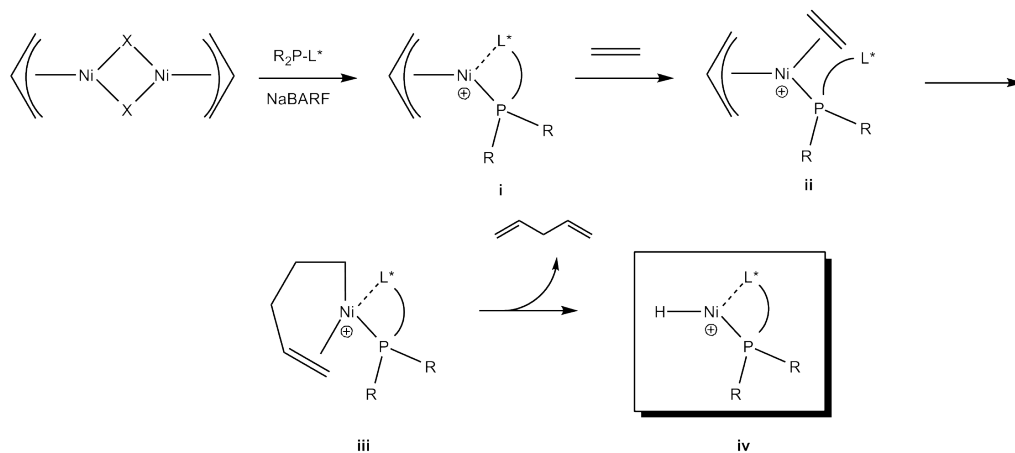


Figure 3: Generation of the Active Catalyst

The active catalyst is generated by mixing $[(\text{allyl})\text{NiBr}]_2$, a ligand containing a hemilabile moiety (L^*), and a weakly coordinating counterion like sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) in a non-coordinating solvent such as dichloromethane. The 16 electron cationic nickel precatalyst **i** is exposed to an atmosphere of ethylene which causes the formation of **ii** and subsequent insertion of ethylene to form intermediate **iii**. The intermediate **iii** undergoes β -hydride elimination to form 1,4-pentadiene and the proposed active catalyst species **iv**. After the active catalyst has been generated, the vinyl arene substrate **v** is introduced to the solution. The vinyl arene coordinates to the catalyst and the hydride is transferred to the terminal position of the alkene. This allows a stabilized η^3 complex **vii** to form with the aromatic system, as opposed to an η^1 complex that would be formed if the hydride were transferred to the internal position of the alkene. The regioselectivity of the reaction, the formation of branched vs. linear products, is thought to be controlled by the stability of the η^3 complex.¹¹ It is also possible for ethylene to bind to the catalyst in place of the vinyl arene which would lead to ethylene oligomers. The ethylene concentration and catalyst loading are such that the formation of ethylene oligomers is not

observed. In the subsequent step the hemilabile portion of the ligand (L^*) detaches to allow for the coordination of ethylene and formation of **viii**. The reaction fails if a coordination site is not available for ethylene at this step, but may also fail without the extra stabilization of the nickel by the hemilabile group.⁹ The formation of **viii** could ostensibly occur with another molecule of the substrate leading to the formation of oligomers, however the size of the ligand hinders the position allowing ethylene to coordinate preferentially. Ethylene selectively inserts into the substrate to form **ix** which undergoes β -hydride elimination to provide the desired product **x** and regenerate the catalyst. If the reaction conditions are not carefully controlled, the product **x** can undergo a nickel mediated isomerization reaction to form both the E and Z isomers of olefin **xi**. The formation of a conjugated double bond is presumably the driving force for isomerization.

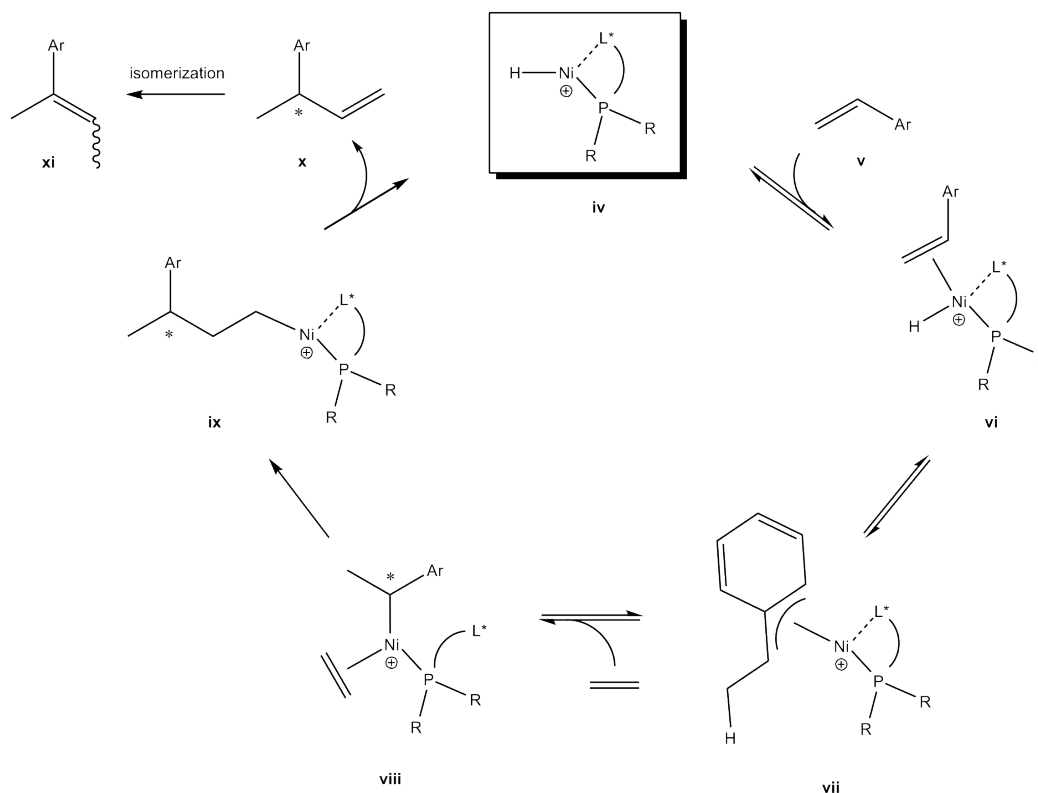


Figure 4: Catalytic Cycle

1.3 Diastereoselectivity and Internal Control

When a chiral molecule reacts to introduce additional sources of chirality, products may be formed that are no longer related as mirror images. Compounds containing the same connectivity that are

not related as mirror images are referred to as diastereomers. As an example, the aldol reaction generates two new chiral centers and illustrates how a mixture of both diastereomers and enantiomers can form. The number of possible products is equal to 2^n , where n is equal to the number of chiral centers or sources of chirality in the molecule. Figure 5 below shows the products of a cross aldol reaction and their stereochemical relationship. The enantiomers have the configuration at both chiral centers inverted, whereas the diastereomers only differ by the configuration at one of the chiral centers.

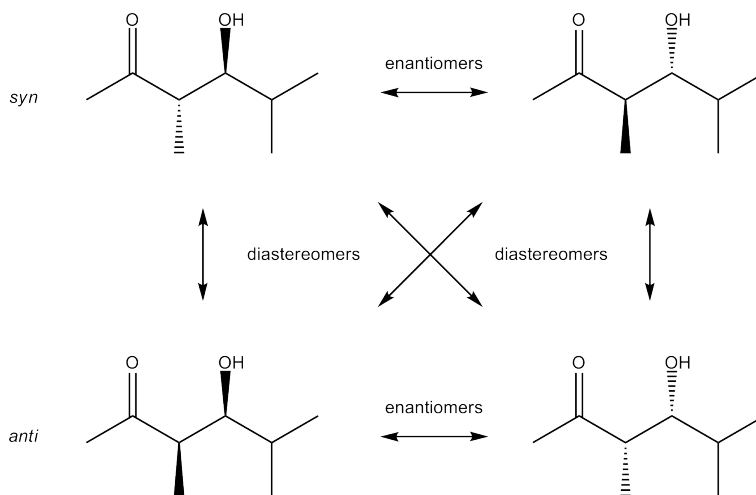


Figure 5: Stereochemical Relationships

Chirality is only produced selectively within chiral environments; therefore, chiral reagents must be utilized or the substrate of the reaction must contain an existing form of chirality to obtain selectivity. When the aforementioned aldol reaction is carried out in the presence of the chiral α -amino acid L-proline the reported diastereoselectivity and enantioselectivity are excellent.¹³ It is the major thrust of this project to examine the level of selectivity obtained by a number of different simple olefin transformations using achiral reagents and chiral substrates obtained from the hydrovinylation reaction. In order for reasonable levels of asymmetric induction to be obtained when the substrate provides the directing chiral center several requirements must be met.¹⁴ First, the directing chiral center should be within one or two bonds of the prochiral center so that it is close enough to interact with an incoming reagent. The proximity requirement will generally hold true, however exceptions do exist. Secondly, there should only be one energetically favorable conformation or reactive conformation at the chiral center. Finally, sufficient differences must exist between conformations and these differences could be imparted by the groups attached to the chiral

center. The groups at the chiral center can differ in their steric bulk, have a stereoelectronic effect, or can have the ability to coordinate with the incoming reagent and direct it to a specific face.

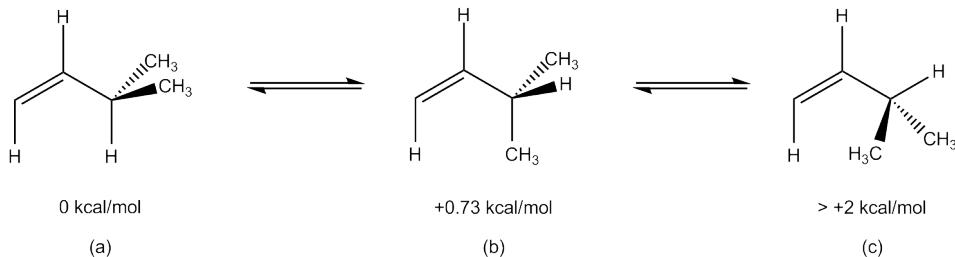


Figure 6: Calculated Conformational Minima of 3-methyl-1-butene

The most energetically favorable conformation of molecules containing an olefin moiety will typically be governed by allylic 1,3-strain. Ab initio DFT/MP2 calculations with a 6-31G* basis set for 3-methyl-1-butene (fig. 6) predicts the most stable conformation to be 6a, where the two methyl groups bisect the adjacent hydrogen.¹⁵ In 4-methyl-2-pentene (fig. 7) the most stable conformation is 7a, which occurs again when the two methyl groups bisect the adjacent hydrogen. In the latter case the addition of a methyl group at the 1 position of the olefin increases the rotational barrier by introducing additional allylic 1,3-strain. In general the most stable conformation places the two largest substituents at the 3 position in an orientation where they bisect the group at the 2 position, leaving the smallest group eclipsed with the 1 position.

$$\Delta G = -RT \ln(K_{eq}) \quad (1)$$

$$K_{eq} = e^{-\frac{\Delta G}{RT}}$$

Assuming an equilibrium exists between the two most stable conformations, the equilibrium constant can be determined using equation 1 and the energy difference. At room temperature (298.15 K) with an energy difference of 0.73 kcal/mol approximately 78% of 3-methyl-1-butene will exist as 6a and 22% will exist as 6b. When the energy difference jumps to only 3.44 kcal/mol roughly 99.7% of 4-methyl-2-pentene exists as 7a and 0.03% exists as 7c. For 99.99% of molecules to exist in the thermodynamically favored conformation an energy difference of 5.46 kcal/mol is required, a remarkably small value considering the enthalpy of a carbon carbon single bond is 82.7 kcal/mol.¹⁶ Ab initio DFT/MP2 calculations using a 6-31G* basis set for the two hydrovinylation adducts used in this project agreed with what would be expected when considering allylic 1,3-strain. The energy

minima discovered for both resulted in the two largest groups bisecting the adjacent hydrogen. The rotational barriers and energies of other conformational minima were not calculated.

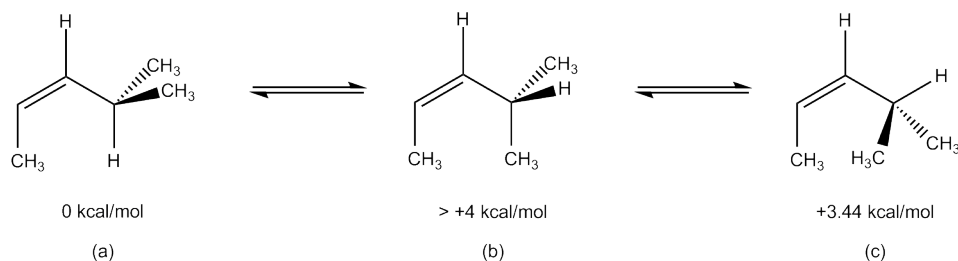


Figure 7: Calculated Conformational Minima of 4-methyl-2-pentene

After determining the minimum energy conformation, the relative steric bulk of the groups attached at the chiral center can be used to make predictions about the dominant face of attack. Electrophilic reagents will prefer to approach the olefin moiety from above or below the plane due to the higher concentration of relatively loosely held electron density in this region. Assuming sufficient differences between the groups on either side of the plane, the reagent will prefer to approach the olefin from the less hindered face. For the substrate (S)-1-(but-3-en-2-yl)-4-isobutylbenzene (fig.

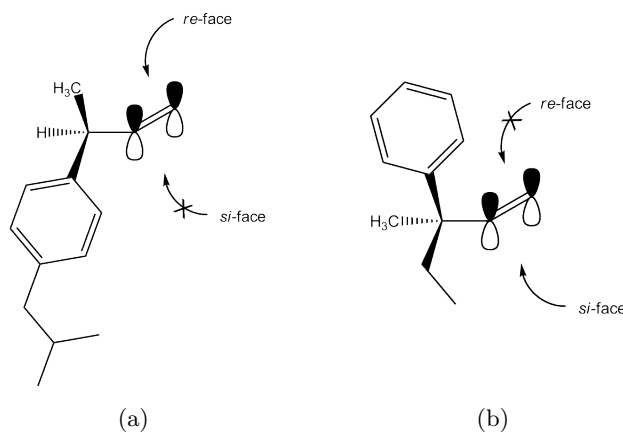


Figure 8: Proposed Face of Attack

8a) the the *re*-face is the favored pathway of attack because it is hindered only by a methyl group, whereas the *si*-face is hindered by a larger aromatic group. In (R)-(3-methylpent-1-en-3-yl)benzene (fig. 8b) the *si*-face is favored using this model. Even with these predictive methods it is impossible to deduce *a priori* what level of selectivity can be obtained and can even be difficult to definitively determine which face will be favored. The rotational barriers in these molecules are typically not high enough to lock into a specific conformation and other structural or electronic factors may contribute to the direction of attack.

2 Transformations

2.1 Synthetic Strategy

The intent of this project is to examine the level of diastereoselectivity obtained when molecules containing a chiral center installed by the hydrovinylation reaction are treated with achiral reagents. Starting from the commercially available aldehydes and ketones the desired starting materials for investigation are prepared in two steps. The Wittig reaction is used to convert the carbonyl compounds to electron rich styrene derivatives that then readily undergo hydrovinylation under recently developed conditions.¹⁷ Using well known procedures the hydrovinylation adducts are converted to epoxides, diols, internal alcohols, and bromohydrins to evaluate selectivity across a range of transformations.

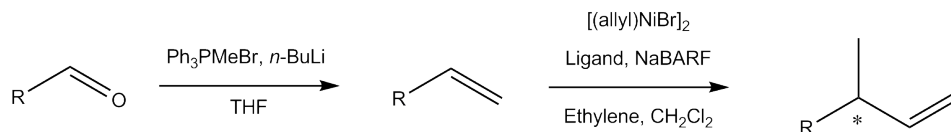


Figure 9: Synthetic Strategy from Commercially Available Compounds

2.2 Basic Olefin Transformations

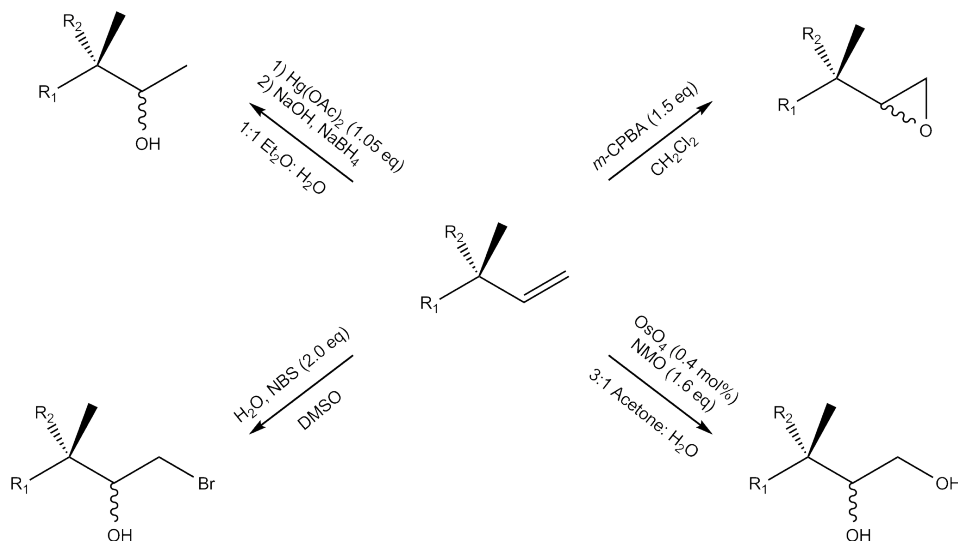


Figure 10: Overview of Olefin Transformations

	R ₁	R ₂
(3) (S)-1-(but-3-en-2-yl)-4-isobutylbenzene	4-isobutylphenyl	H
(4) (R)-(3-methylpent-1-en-3-yl)benzene	Ph	Et

Table 1: Substrate Scope

2.2.1 Epoxidation

The epoxidation of olefins using *meta*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane provided the desired epoxide products in high yields and poor diastereoselectivities. Olefins **3** and **4** afforded the epoxide products with 1 %de and 5 %de respectively. The reaction has been proposed to proceed through a concerted pericyclic mechanism where the peroxide bond is cleaved and the terminal oxygen is simultaneously transferred to the olefin in a stereospecific fashion.¹⁸ The *m*-CPBA reagent has little steric demand since it is essentially planar, which may provide justification for the low observed diastereoselectivities.

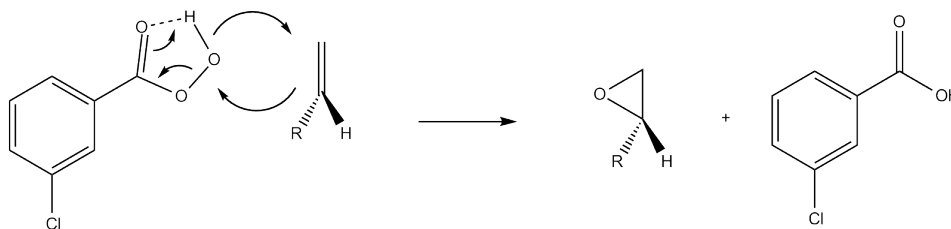


Figure 11: Bartlett Concerted Mechanism of Epoxidation

2.2.2 Dihydroxylation

Osmium tetroxide mediated dihydroxylation afforded the expected products in high yield and moderate diastereoselectivity. Olefins **3** and **4** resulted in diastereoselectivities of 33 %de and 64 %de respectively. Due to the highly expensive and toxic nature of osmium tetroxide, the reaction was performed with a catalytic amount in the presence of the stoichiometric reoxidant N-methylmorpholine-N-oxide. The reaction was originally believed to occur by way of a [3+2] addition followed by the oxidative cleavage or hydrolysis of the osmate ester.¹⁹ By analogy to chromyl chloride mediated oxidation of olefins, the mechanism was reconsidered and proposed to begin with a [2+2] addition to the more electrophilic osmium center.²⁰ More recent theoretical and empirical evidence suggests that the reaction does indeed proceed through the originally proposed [3+2] mechanism.²¹ The [2+2] mechanism would require a closer approach between the osmium center

and the olefin which could lead to higher levels of selectivity. The moderate levels of selectivity seen with osmium tetroxide may be a direct result of the size of the osmium reagent and the approach that is required to accomodate the large third row transition metal. Osmium has an experimental atomic radius of 130 pm, nearly twice that of the 70 pm radius of carbon and more than double the 60 pm oxygen radius.²²

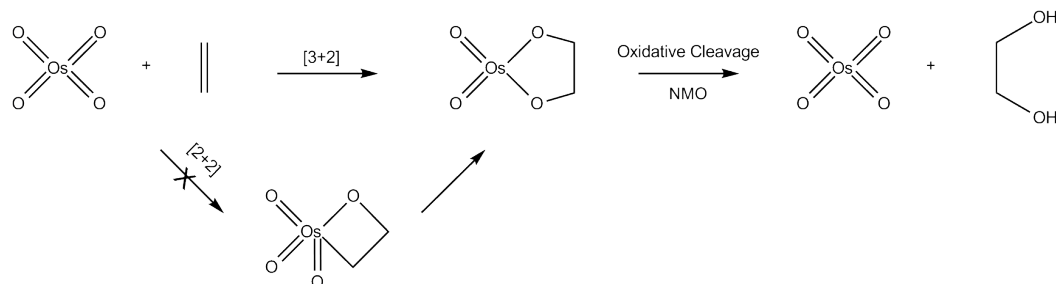


Figure 12: Proposed Pathway for Osmium Tetroxide Dihydroxylation

2.2.3 Oxymercuration

The oxymercuration-reduction reaction sequence provided both Markovnikov alcohol products again with moderate diastereoselectivity. The alcohol from olefin **3** was obtained with a 43 %de and olefin **4** gave a slightly higher 48 %de. The conditions chosen for the reaction resulted in low isolated yields and substantial recovery of starting material. In a typical setup, the reaction is performed using a two phase solvent system consisting of ether and water.²³ The mercury source, typically mercuric acetate, is dissolved in water and stirred into an ethereal solution of olefin. With a solvent system of 1:1 diethyl ether: water slow reaction times were observed even in the presence of an acid catalyst. After complete mercuration, the reduction was preformed slowly at reduced temperatures but still gave back an appreciable amount of starting material. In the literature oxymercuration-reduction of styrene, the yield of 1-phenylethanol as checked by gas chromatography was consistently around 90% even when the reaction mixture was heated to approximately 60°C and reduced.²⁴ The mechanism of the oxymercuration reaction proceeds through a mercurinium ion that undergoes anti attack at the Markovnikov position.²⁵ The observed regiochemistry is a consequence of carbocation character developing at the transition state which is stabilized by the electron donating nature of adjacent alkyl substituents. Mercury has a large atomic radius, approximately 150 pm,²² which again may help to impart the somewhat higher levels of diastereoselectivity

observed in this reaction.

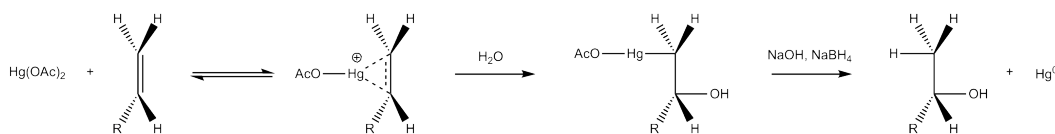


Figure 13: Mechanism of Oxymercuration

2.2.4 Bromohydroxylation

The bromohydrin reaction did not proceed cleanly, but instead produced what is believed to be a mixture of multiple regioisomeric products for both substrates. Mechanistic studies indicate that the reaction proceeds through a bromonium ion that could potentially open to a α -bromocarbonium ion.²⁶ Isotopic labeling indicates the alcohol oxygen is transferred to the substrate by dimethylsulfoxide which is used as the reaction solvent. The resulting bromodimethylsulfoxonium ion is hydrolyzed by water present in the solution to give the alcohol and the molecule of dimethylsulfoxide back. For the majority of substrates studied in the literature the bromonium ion opened away from the more substituted side of the olefin to yield the Markovnikov alcohol. In certain cases the opposite regiochemistry was observed, and in others a mixture of both possible regiochemistries was observed. For olefin **3** gas chromatographic analysis indicated that five major products formed.

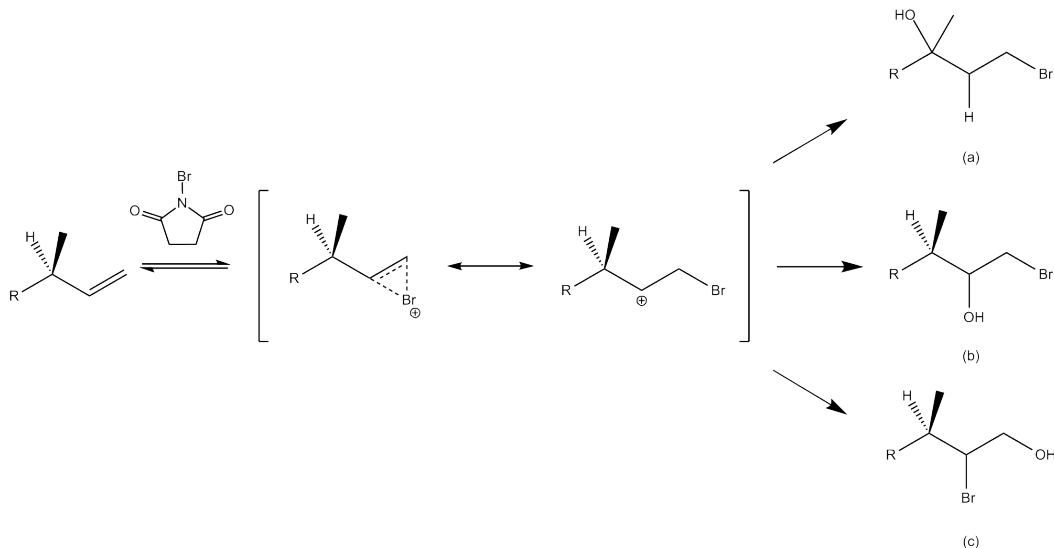


Figure 14: Proposed Products of Bromohydroxylation

Although only speculation, figure 14 illustrates the most likely product distribution. Bromohydrin a (figure 14) results from a hydride shift to rearrange to the more stable conjugated tertiary carbo-

nium ion which is quenched by dimethylsulfoxide to yield a racemic mixture of the β -bromohydrin. Bromohydrins b and c (figure 14) contain mixtures of two diastereomers, accounting for the remaining four products.

2.3 The Barton Reaction

The hydrovinylation reaction has been shown to work poorly with internal olefins, however when terminal olefins are used an unfunctionalized methyl group will always result.¹⁷ A search of the literature yields few results for reactions capable of selectively functionalizing the resulting methyl group. The Barton reaction was briefly investigated as a route to functionalize the methyl group that results from the hydrovinylation of terminal olefins. In the Barton reaction an alkyl nitrite prepared from the terminal alcohol by reaction with nitrosonium tetrafluoroborate or nitrosyl chloride is photolytically cleaved.²⁷ The resulting oxygen radical can abstract a δ hydrogen by way of a 6-membered transition state leaving an alkyl radical. The nitroso radical left from the initial homolysis combines with the alkyl radical to produce a δ -nitroso alcohol which readily tautomerizes to the corresponding oxime.

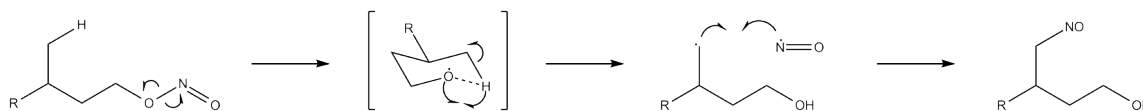


Figure 15: Barton Reaction Mechanism

To maintain an anhydrous reaction environment all glassware was flame dried under vacuum and both benzene and the alkyl nitrite were distilled. Oxygen was excluded from the reaction by flushing with dry nitrogen and withdrawing the atmosphere with a syringe. Under these conditions the photolysis appeared to be complete by thin layer chromatography analysis within 3 hours. By comparing infrared data with the literature the crude reaction mixture appeared to contain an oxime moiety. In the original literature an absorption at 1635 cm^{-1} was reported.²⁷ The crude reaction mixture showed a weak absorption at 1633 cm^{-1} , indicative of the oxime stretch. The proton NMR and infrared data obtained both clearly indicate that the nitrite was converted to an alcohol. The oxime proved to be difficult to purify and may have decomposed on the silica when running a preparatory TLC plate. Direct conversion to the aldehyde by acid hydrolysis may prove to be the most effective method to recover the product and experiments to this effect are ongoing.

3 Conclusions

3.1 Summary of Results

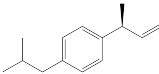
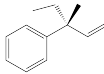
		
	3	4
Epoxidation	1	5
Dihydroxylation	33	64
Bromohydroxylation	-	-
Oxymercuration	43	48

Table 2: Summary of Diastereoselectivities (%de)

3.2 Future Work

To further enhance diastereoselectivities the absolute configuration of the major product for each substrate should be determined to develop an accurate model that explains the observed selectivity. With a working model in hand, the reagents and reaction conditions could be tuned to exploit the properties of the system responsible for diastereocontrol. The absolute configurations would need to be determined by either analogy to literature compounds, NMR techniques, or X-Ray analysis of solid derivatives. Obtaining exceptionally high levels of diastereoselectivity may ultimately require the introduction of other chiral reagents with a stereochemical match to the substrate. An asymmetric variant of the dihydroxylation reaction utilizing a chiral amine ligand has already been developed and won a portion of the 2001 Nobel Prize in chemistry.²⁸ The asymmetric dihydroxylation and other similar reactions could have the potential to achieve high levels of control.

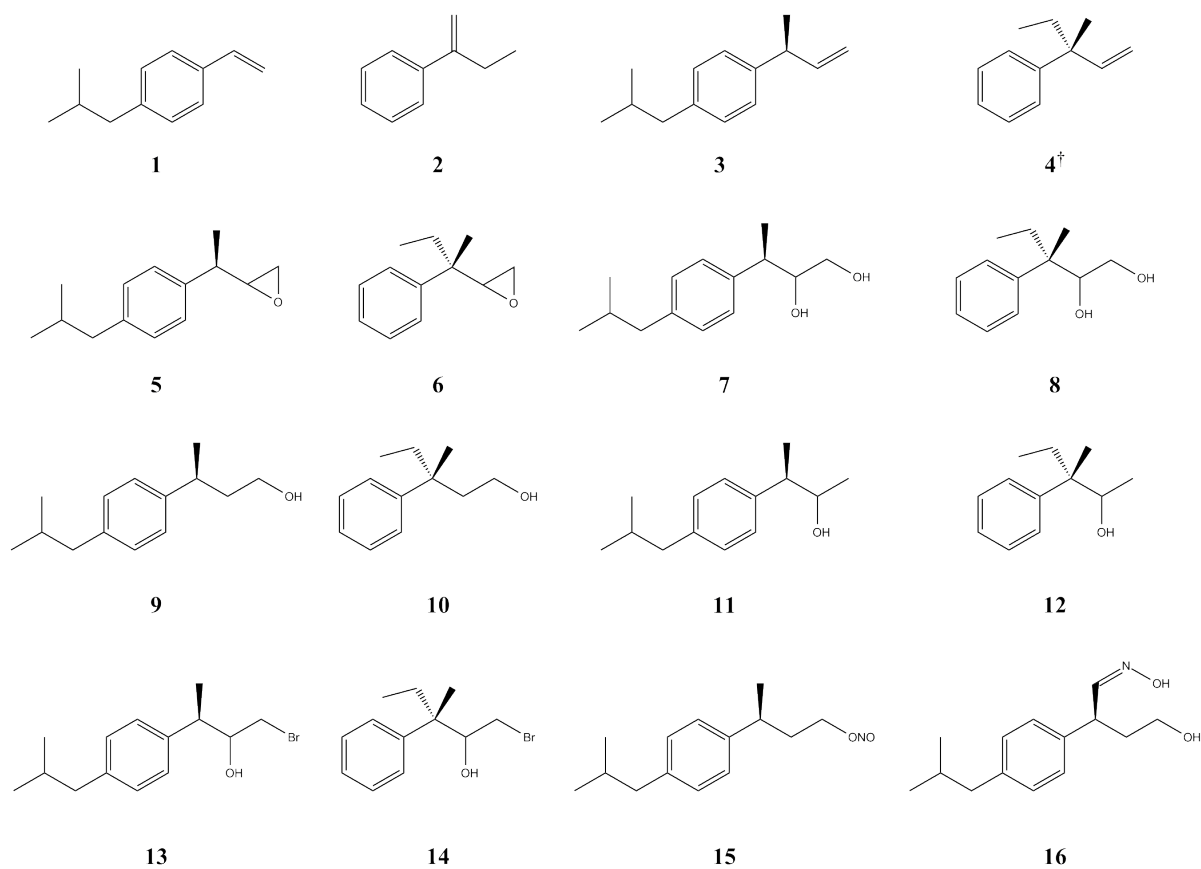
The preliminary investigation of the Barton reaction appears to indicate that there may be some hope of functionalizing methyl groups resulting from the hydrovinylation of terminal olefins. Functionalization by this route requires hydrovinylation, hydroboration, nitrite formation, and photolysis to acquire the oxime. Although this may appear to be a large number of steps, alternative routes are likely to be longer, especially if enantiopure derivatives are desired. Further work needs to be done to characterize the oxime. The infrared spectrum is convincing and matches well with the original literature, yet the proton and carbon NMR data are not definitive. Isolation of the pure oxime was challenging and work is currently underway to convert the oxime directly to the aldehyde by acidic hydrolysis. Once in hand, the aldehyde should be trivial to purify and fully characterize.

4 Experimental

4.1 General Methods

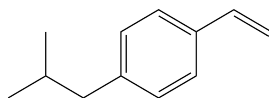
Air sensitive reactions were performed using Schlenck techniques under nitrogen that had been passed through a Drierite[®] tower. Ethylene (99.5%) was purchased from Matheson Inc. and passed through a tube of Drierite[®] before use. A Vacuum Atmospheres drybox containing a nitrogen atmosphere was used where mentioned for particularly air and moisture sensitive manipulations. Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone ketyl. Benzene was distilled under nitrogen from sodium metal. Dichloromethane was distilled under nitrogen from calcium hydride. Internal reaction temperatures were monitored with a digital thermometer (Omega Instruments Digicator Model 400A). Analytical TLC was performed on E. Merck precoated (0.25 mm) silica gel 60 F₂₅₄ plates. Preparatory TLC was performed on 20x20cm Analtech Uniplat precoated (1 mm) silica gel GF plates. Flash column chromatography was performed with Scientific Adsorbents Incorporated Microns Flash silica gel 40. NMR spectra (¹H, ¹³C) were recorded on a Bruker AM-250 spectrometer using CDCl₃ as the solvent. Chemical shifts were measured in parts per million (δ) relative to CDCl₃ (δ = 7.26) for ¹H and (δ = 77.16) for ¹³C. Multiplicities are reported as: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), qd (quartet of doublets). Coupling constants (*J* values) are given in units of Hz. Gas chromatographic analysis was performed on a Hewlett-Packard 5890 equipped with a flame ionization detector connected to a HP 3396 integrator using helium as the carrier gas. An HP-ultra-1 crosslinked methyl silicone capillary column (25 m x 0.2 mm x 0.33 μ m film thickness) was used for all separations. All compounds containing free hydroxyl groups were treated with N,O-bis(trimethylsilyl)acetamide prior to injection to protect the alcohol as the TMS ether. Photochemical reactions were carried out in a Rayonet RPR-100 photochemical reactor equipped with medium pressure ultraviolet lamps.

4.2 List of Compounds Prepared During This Study



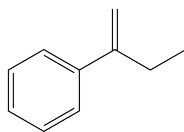
[†]Compound was provided courtesy of C. R. Smith.

4.3 Experimental Procedures



1

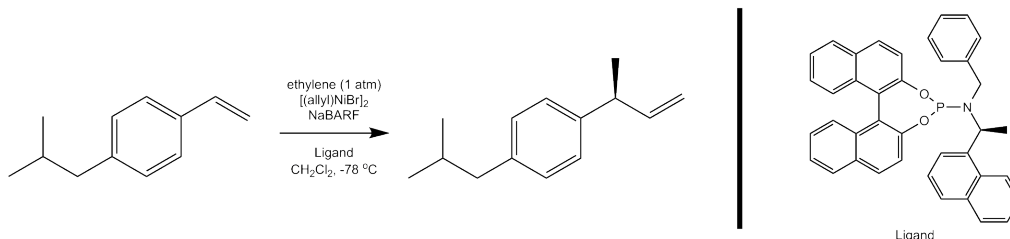
1-isobutyl-4-vinylbenzene (1). A 50 mL 3-neck round bottom flask equipped with a gas-inlet, pressure equalizing additional funnel with rubber septum, and glass stopper was flame dried under vacuum, purged with nitrogen, and charged with methyl triphenyl phosphonium bromide (1.0781 g, 3.0180 mmol). Still dried THF (9.0 mL) was added via syringe and the resulting solution was stirred for 30 minutes at room temperature. Under a strong stream of nitrogen n-butyl lithium (1.2 mL, 3.0 mmol) was added in a single portion which caused the solution to become translucent red-orange. After stirring for an additional two hours the addition funnel was charged with 4-isobutyl-benzaldehyde (0.42 mL, 2.5 mmol) and 1.5 mL of dry THF. The contents of the addition funnel were added in a single portion and rinsed into the reaction mixture with two 1.0 mL aliquots of dry THF. The reaction appeared to be complete by TLC (1:3 ethyl acetate: hexanes) after 15 minutes. The flask was poured into 20 mL of ice cold 1:1 ether: pentane, filtered through a pad of Celite[®] and concentrated *in vacuo* to provide a colorless crude oil. Purification *via* flash column chromatography (pentane) provided alkene **1** as a colorless oil (0.3420 g, 86%). R_f 0.76 (1:3 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.33 (d, 2H, J 8 Hz), 7.11 (d, 2H, J 8 Hz), 6.71 (dd, 1H, J 17.5 Hz, 10.8 Hz), 5.71 (d, 1H, J 17.5 Hz), 5.20 (d, 1H, J 10.8 Hz), 2.47 (d, 2H, J 7 Hz), 1.87 (m, 1H), 0.913 (d, 6H, J 6.5 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 141.44, 136.71, 135.02, 129.22, 125.91, 112.72, 45.12, 30.16, 22.30.



2

but-1-en-2-ylbenzene (2). A 50 mL 3-neck round bottom flask equipped with a reflux condenser topped with a gas-inlet, pressure equalizing addition funnel with rubber septum, and glass stopper was flame dried under vacuum, purged with nitrogen, and charged with methyl triphenyl phosphonium bromide (1.0748 g, 3.0088 mmol). Still dried THF (9.0 mL) was added via syringe

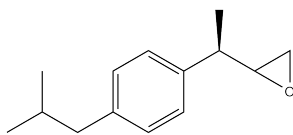
and the resulting solution was stirred for 30 minutes at room temperature. Under a strong stream of nitrogen n-butyl lithium (1.2 mL, 3.0 mmol) was added in a single portion which caused the solution to become translucent red-orange. After stirring for an additional two hours the addition funnel was charged with propiophenone (0.33 mL, 2.5 mmol) and 1.5 mL of dry THF. The contents of the addition funnel were added in a single portion and rinsed into the reaction mixture with two 1.0 mL aliquots of dry THF. The contents of the flask became an opaque yellow color and after bringing to reflux the solution again became translucent. After refluxing for 20 hours the contents of the flask were poured into 20 mL of ice cold 1:1 ether: pentane, filtered through a pad of Celite[®] and concentrated *in vacuo* to provide a light yellow crude oil. Purification *via* flash column chromatography (pentane) provided alkene **2** as a colorless oil (0.2457 g, 75%). R_f 0.75 (1:3 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.44-7.26 (m, 5H), 5.29 (s, 1H), 5.07 (t, 1H, J 1.2 Hz), 2.53 (2H, qd, J 7.4 Hz, 0.8 Hz), 1.12 (3H, td, J 7.4 Hz, 1 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 150.00, 141.59, 128.17, 127.2, 125.96, 110.86, 28.00, 17.89.



3

(S)-1-(but-3-en-2-yl)-4-isobutylbenzene (3). A 50 mL 3-neck round bottom flask equipped with a flow controlled gas-inlet, temperature probe, rubber septum, and magnetic stir-bar was flame dried under vacuum and purged with dry nitrogen. Inside of a dry box [(allyl)NiBr]₂ (5.0 mg, 0.014 mmol), ligand (14.4 mg, 0.0280 mmol), NaBARF (24.8 mg, 0.0280 mmol), and alkene **1** (0.3255 g, 2.031 mmol) were weighed into separate vials. The [(allyl)NiBr]₂ and ligand were each suspended in 1 mL of dichloromethane, the NaBARF was suspended in 2 mL of dichloromethane, and alkene **1** was suspended in 4 mL of dichloromethane. The dark red [(allyl)NiBr]₂ solution was transferred *via* glass pipet to the solution of ligand followed by a 1 mL rinse. The resulting solution was transferred to the solution of NaBARF followed by a 1 mL rinse. The previously flame dried flask was charged with 10 mL of still dried dichloromethane and after standing for 1.5 hrs the precatalyst solution was transferred *via* cannula followed by 4 mL of rinsings. A dry ice

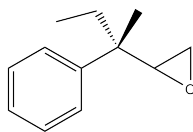
acetone bath was used to bring the internal temperature to -78°C at which point the flow controlled adapter was shut off and a purging ethylene line was inserted with a needle through the rubber septum. A syringe was used to withdraw approximately 60 mL of the atmosphere. After stirring the catalyst solution for 1 minute alkene **1** was introduced dropwise *via* syringe followed by 2 mL of rinsings. The reaction was maintained at -78°C for 2 hours then quenched with 2 mL of water and warmed to room temperature. The yellow solution was poured into 40 mL of water, the dichloromethane was drained, and the aqueous layer extracted with dichloromethane (3x 20 mL). The organic extracts were combined, dried over magnesium sulfate, and purified *via* flash column chromatography (pentane) to afford alkene **3** as a colorless liquid (0.3775 g, 98.69%). R_f 0.48 (pentane); ^1H NMR (250 MHz, CDCl_3) δ_H 7.14-7.06 (m, 4H), 6.11-5.94 (m, 1H), 5.09-5.00 (m, 2H), 3.54-3.38 (m, 1H), 2.45 (d, 2H, J 7 Hz), 1.85 (sept, 1H, J 6.7 Hz), 1.36 (d, 3H, J 7 Hz), 0.91 (d, 6H, J 6.5 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 143.71, 142.90, 139.57, 129.26, 127.04, 112.99, 45.20, 42.96, 30.39, 22.57, 20.90.



5

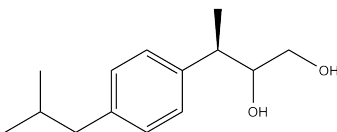
2-((R)-1-(4-isobutylphenyl)ethyl)oxirane (5) A 5 mL single neck round bottom flask equipped with a magnetic stir-bar was charged with alkene **3** (62.8 mg, 0.333 mmol) and 1.4 mL of dichloromethane then chilled to near 0°C in a salt-ice water bath. To the stirred solution *meta*-chloroperoxybenzoic acid (70-75% w/w) (0.1261 g, 0.5298 mmol) was added in a single portion. The flask was fit with a plastic stopper and the resulting cloudy white suspension was brought to room temperature at which point it became clear. After 7 hours the solution had again become cloudy and was diluted with 75 mL of dichloromethane, washed once with 50 mL of 15% (v/v) sodium metabisulfite solution, followed by 50 mL of saturated sodium bicarbonate. The dichloromethane was dried over magnesium sulfate and concentrated *in vacuo* to afford a crude yellow oil which was purified *via* flash column chromatography (1:10 ether: pentane) to provide epoxide **5** as a clear oil (63.5 mg, 93.2%). R_f 0.33 (1:10 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.23-7.04 (m, 4H), 3.13-2.94 (m, 1H), 2.81-2.55 (m, 3H), 2.45 (d, 2H, J 7.2 Hz), 1.86 (sept, 1H), 1.42-1.28 (m, 3H), 0.90 (d, 6H, J 6.5 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 140.09, 139.95, 139.79, 129.2, 129.13,

127.07, 126.98, 57.08, 56.46, 46.95, 45.85, 44.97, 42.04, 40.91, 30.16, 22.34, 17.74, 16.78.



6

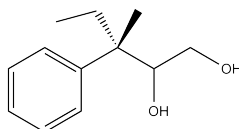
2-((S)-2-phenylbutan-2-yl)oxirane (6) A 5 mL single neck round bottom flask equipped with a magnetic stir-bar was charged with alkene **4** (53.0 mg, 0.331 mmol) and 1.4 mL of dichloromethane then chilled to near 0°C in a salt-ice water bath. To the stirred solution *meta*-chloroperoxybenzoic acid (70-75% w/w) (0.1260 g, 0.5294 mmol) was added in a single portion. The flask was fit with a plastic stopper and the resulting cloudy white suspension was brought to room temperature at which point it became clear. After 7 hours the solution had again become cloudy and was diluted with 75 mL of dichloromethane, washed once with 50 mL of 15% (v/v) sodium metabisulfite solution, followed by 50 mL of saturated sodium bicarbonate. The dichloromethane was dried over magnesium sulfate, concentrated *in vacuo*, and purified *via* preparatory thin-layer chromatography (1:10 hexanes: ethyl acetate) to yield epoxide **6** as a yellow oil (54.2 mg, 93.0%). R_f 0.33 (1:10 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.42-7.18 (m, 5H), 3.19-3.01 (m, 1H), 2.76-2.68 (m, 1H), 2.67-2.52 (m, 1H), 2.00-1.61 (m, 2H), 1.32-1.15 (m, 3H), 0.85-0.71 (m, 3H); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 144.81, 144.07, 128.15, 128.02, 126.84, 126.54, 126.14, 59.47, 58.98, 44.27, 43.92, 41.23, 41.11, 31.01, 30.46, 20.02, 19.67, 8.36, 8.20.



7

(R)-3-(4-isobutylphenyl)butane-1,2-diol (7) A 10 mL single neck pear-shaped flask equipped with a magnetic stir-bar was charged with alkene **3** (62.5 mg, 0.332 mmol), 0.13 mL of acetone, and 0.04 mL of water. To the stirred solution 4-methylmorpholine N-oxide monohydrate (76.2 mg, 0.564 mmol) was added in a single portion and the flask was chilled on a salt-ice water bath. From a previously prepared 0.15 M aqueous solution, osmium tetroxide (0.01 mL, 0.0015 mmol) was added as a single drop from a 21 gauge syringe needle. The flask was sealed with a plastic stopper and

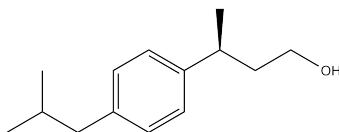
brought to room temperature. After stirring for 5.5 hours the solution became homogeneous and brown. The reaction was diluted with 0.2 mL of dichloromethane, chilled with a salt-ice water bath, and sodium metabisulfite (97.2 mg, 0.511 mmol) was added in a single portion. After warming to room temperature the solution became an opaque peach color and was stirred for an additional 30 minutes. Sodium sulfate (17.3 mg, 0.122 mmol) was added and the viscous peach-colored solution was stirred for 30 more minutes. The contents of the flask were gravity filtered and thoroughly rinsed with acetone then concentrated *in vacuo* to provide a clear oil which was dissolved in 15 mL of ethyl acetate. The ethyl acetate was washed with 10 mL of water, 10 mL of 0.25N sulfuric acid, 10 mL of brine, and filtered through a short plug of silica in a Pasteur pipet. The solvent was removed *in vacuo* and the resulting oil was concentrated from two small aliquots of benzene under reduced pressure to afford diol **7** as a viscous dark orange oil (68.4 mg, 92.7%). R_f 0.42 (ethyl acetate); ^1H NMR (250 MHz, CDCl_3) δ_H 7.19-7.04 (m, 4H), 3.82-3.28 (m, 3H), 2.91-2.70 (m, 1H), 2.50-2.40 (m, 2H), 1.94-1.72 (m, 1H), 1.49-1.21 (m, 3H), 0.95-0.82 (m, 6H); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 140.64, 140.31, 140.00, 129.44, 129.26, 127.57, 127.14, 76.73, 76.28, 65.07, 64.51, 44.95, 42.49, 42.34, 30.13, 22.33, 17.76, 17.26.



8

(S)-3-methyl-3-phenylpentane-1,2-diol (8) A 10 mL single neck pear-shaped flask equipped with a magnetic stir-bar was charged with alkene **4** (56.7 mg, 0.354 mmol), 0.13 mL of acetone, and 0.04 mL of water. To the stirred solution 4-methylmorpholine N-oxide monohydrate (75.6 mg, 0.559 mmol) was added in a single portion and the flask was chilled on a salt-ice water bath. From a previously prepared 0.15 M aqueous solution, osmium tetroxide (0.01 mL, 0.0015 mmol) was added as a single drop from a 21 gauge syringe needle. The flask was sealed with a plastic stopper and brought to room temperature. After stirring for 24 hours the solution became homogeneous and brown. The reaction was diluted with 0.2 mL of dichloromethane, chilled with a salt-ice water bath, and sodium metabisulfite (101.1 mg, 0.5318 mmol) was added in a single portion. After warming to room temperature the solution became an opaque peach color and was stirred for an additional 30 minutes. Sodium sulfate (16.5 mg, 0.116 mmol) was added and the viscous peach-colored solution

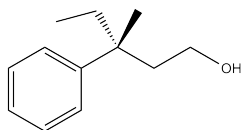
was stirred for 30 more minutes. The contents of the flask were gravity filtered and thoroughly rinsed with acetone then concentrated *in vacuo* to provide a clear oil which was dissolved in 15 mL of ethyl acetate. The ethyl acetate was washed with 10 mL of water, 10 mL of 0.25N sulfuric acid, 10 mL of brine, and filtered through a short plug of silica in a Pasteur pipet. The solvent was removed *in vacuo* and the resulting oil was concentrated from two small aliquots of benzene under reduced pressure to afford diol **8** as a viscous brown oil (58.5 mg, 85.1%). R_f 0.50 (ethyl acetate); ^1H NMR (250 MHz, CDCl_3) δ_H 7.36-7.26 (m, 5H), 3.80-3.29 (m, 3H), 2.09-1.50 (m, 2H), 1.35-1.20 (m, 3H), 0.69-0.61 (m, 3H); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 143.78, 143.70, 128.35, 127.13, 126.87, 126.24, 126.11, 79.81, 79.73, 63.15, 63.04, 44.87, 44.51, 30.83, 30.24, 18.36, 17.61, 8.20, 8.01.



9

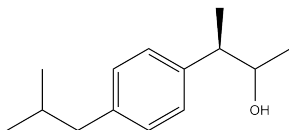
(S)-3-(4-isobutylphenyl)butan-1-ol (9) A 25 mL 3-neck round bottom flask equipped with a magnetic stir-bar, gas-inlet, glass stopper, and temperature probe was flame dried under vacuum, purged with nitrogen, and charged with alkene **3** (0.5073 g, 2.694 mmol) which was rinsed into the flask using 6.7 mL of still dried THF. To the stirred solution 9-borabicyclo[3.3.1]nonane dimer (0.9187 g, 3.765 mmol) was added under a strong stream of nitrogen in a single portion. The solution was stirred for 18 hours at room temperature then chilled to -5°C and the glass stopper was replaced with a rubber septum. Through the septum *via* syringe 4N sodium hydroxide (5.4 mL, 22 mmol) was added slowly followed by 3.4 mL of 30% hydrogen peroxide. The internal temperature was maintained at less than 10°C throughout the course of each addition. The flask was warmed to room temperature and stirred for an additional 30 minutes open to air at which point the solution became filled with a white precipitate. The contents of the flask were transferred to a separatory funnel by rinsing with 20 mL of water then 35 mL of ethyl acetate was added. A solution of 10% sulfuric acid (v/v) was added until the white precipitate had dissolved completely. Approximately 5 mL of acid were required. The aqueous layer was extracted with ethyl acetate (4x 35 mL), dried over magnesium sulfate, and purified by flash column chromatography (1:3 ethyl acetate: hexanes). The resulting oil was dissolved in a small portion of benzene and concentrated

in vacuo to provide alcohol **8** as a cloudy oil (0.5499 g, 2.66 mmol, 98.93%). R_f 0.27 (1:3 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.13-7.05 (m, 4H), 3.56 (td, 2H, J 6.5 Hz, 3 Hz), 2.85 (sext, 1H, J 7.2 Hz), 2.44 (d, 2H, J 7.2 Hz), 1.88-1.52 (m, 4H), 1.27 (d, 3H, J 7 Hz), 0.90 (d, 6H, J 6.8 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 144.10, 139.57, 129.33, 126.74, 61.47, 45.17, 41.21, 36.23, 30.36, 27.55, 22.58.



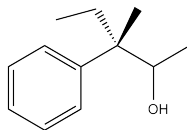
10

(R)-3-methyl-3-phenylpentan-1-ol (10) A 25 mL 3-neck round bottom flask equipped with a magnetic stir-bar, gas-inlet, glass stopper, and temperature probe was flame dried under vacuum, purged with nitrogen, and charged with alkene **4** (0.2040 g, 1.273 mmol) which was rinsed into the flask using 3.2 mL of still dried THF. To the stirred solution 9-borabicyclo[3.3.1]nonane dimer (0.4382 g, 1.796 mmol) was added under a strong stream of nitrogen in a single portion. The solution was stirred for 18 hours at room temperature then chilled to -5°C and the glass stopper was replaced with a rubber septum. Through the septum *via* syringe 4N sodium hydroxide (2.5 mL, 10 mmol) was added slowly followed by 1.6 mL of 30% hydrogen peroxide. The internal temperature was maintained at less than 5°C throughout the course of each addition. The flask was warmed to room temperature and stirred for an additional hour minutes open to air at which point the solution became filled with a white precipitate. The contents of the flask were transferred to a separatory funnel by rinsing with 10 mL of water then 25 mL of ethyl acetate was added. A solution of 10% sulfuric acid (v/v) was added until the white precipitate had dissolved completely. Approximately 2.5 mL of acid were required. The aqueous layer was extracted with ethyl acetate (4x 25 mL), dried over magnesium sulfate, and purified by flash column chromatography (1:2 ethyl acetate: hexanes). The resulting oil was dissolved in a small portion of benzene and concentrated *in vacuo* to provide alcohol **8** as a dark yellow oil (0.1678 g, 73.94%). R_f 0.30 (1:2 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.38-7.15 (m, 5H), 3.62-3.36 (m, 2H), 2.12-1.50 (m, 5H), 1.32 (s, 3H), 0.76-0.62 (m, 3H); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 147.08, 128.34, 126.42, 125.78, 60.04, 45.70, 40.10, 36.17, 23.60, 8.54.



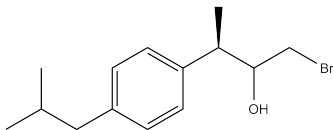
11

(R)-3-(4-isobutylphenyl)butan-2-ol (11) A 10 mL single neck pear shaped flask equipped with a magnetic stir-bar was charged with alkene **3** (64.9 mg, 0.345 mmol) and 0.35 mL of diethyl ether. In a separate 5 mL pear shaped flask equipped with a magnetic stir-bar mercury(II) acetate (0.1180 g, 0.3703 mmol) was added with 0.35 mL of water. The smaller flask was stirred until the mercury(II) acetate had dissolved completely at which point it was transferred in a single portion without rinsing to the larger flask. To the stirred solution approximately 0.02 mL of 60% perchloric acid were added as two drops from a 21 gauge syringe needle. After 10 minutes the solution became pale yellow and upon stirring for an additional hour it had become clear. Thin layer chromatography indicated that the starting material had been fully mercurated. The flask was chilled with an ice bath and 0.17 mL of 6N NaOH was added slowly which immediately caused the solution to turn dark orange. While still cooling the flask 0.35 mL of 0.5M NaBH₄ in 3N NaOH was added slowly. Addition of the NaBH₄ caused the solution to immediately precipitate elemental mercury as a dark grey solid. After complete addition the flask was warmed to room temperature and stirred for an additional 2 hours, filtered through a short plug of Celite[®], and extracted with diethyl ether (4x 1 mL). The ether was dried over magnesium sulfate, concentrated *in vacuo*, and purified *via* flash column chromatography (1:3 diethyl ether: pentane) to yield alcohol **11** as a clear oil (39.9 mg, 53.3%). *R_f* 0.33 (1:3 ethyl acetate: hexanes); ¹H NMR (250 MHz, CDCl₃) δ_H 7.09-7.13 (m, 4H), 3.94-3.75 (m, 1H), 2.75-2.62 (m, 1H), 2.45 (2H, d, *J* 7.2 Hz), 1.85 (sept, 1H, *J* 6.7 Hz), 1.41 (br, 1H), 1.33-1.06 (m, 6H), 0.90 (d, 6H, *J* 6.7Hz); ¹³C NMR (62.9 MHz, CDCl₃) δ_C 140.76, 140.28, 129.51, 129.38, 127.84, 127.65, 72.58, 47.75, 45.18, 30.34, 22.55, 21.10, 20.71, 18.02; See Appendix B for GC traces.



12

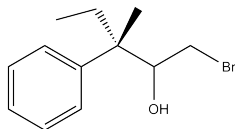
(S)-3-methyl-3-phenylpentan-2-ol (12) A 10 mL single neck pear shaped flask equipped with a magnetic stir-bar was charged with alkene **4** (56.8 mg, 0.354 mmol) and 0.35 mL of diethyl ether. In a separate 5 mL pear shaped flask equipped with a magnetic stir-bar mercury(II) acetate (0.1176 g, 0.3690 mmol) was added with 0.35 mL of water. The smaller flask was stirred until the mercury(II) acetate had dissolved completely at which point it was transferred in a single portion without rinsing to the larger flask. To the stirred solution approximately 0.02 mL of 60% perchloric acid were added as two drops from a 21 gauge syringe needle. After 10 minutes the solution became pale yellow and upon stirring for an additional hour it had become clear. Thin layer chromatography indicated that the starting material had been fully mercurated. The flask was chilled with an ice bath and 0.17 mL of 6N NaOH was added slowly which immediately caused the solution to turn dark orange. While still cooling the flask 0.35 mL of 0.5M NaBH₄ in 3N NaOH was added slowly. Addition of the NaBH₄ caused the solution to immediately precipitate elemental mercury as a dark grey solid. After complete addition the flask was warmed to room temperature and stirred for an additional 2 hours, filtered through a short plug of Celite[®], and extracted with diethyl ether (4x 1 mL). The ether was dried over magnesium sulfate, concentrated *in vacuo*, and purified *via* flash column chromatography (1:3 diethyl ether: pentane) to yield alcohol **12** as a white solid (21.0 mg, 33.2%). R_f 0.29 (1:3 ethyl acetate: hexanes); ¹H NMR (250 MHz, CDCl₃) δ_H 7.40-7.15 (m, 5H), 3.92-3.76 (m, 1H), 2.04-1.59 (m, 2H), 1.38-1.24 (m, 4H), 1.15-0.98 (m, 3H), 0.75-0.60 (m, 3H); ¹³C NMR (62.9 MHz, CDCl₃) δ_C 144.90, 128.49, 128.28, 127.54, 127.32, 126.28, 126.02, 77.36, 75.86, 46.45, 29.98, 18.20, 17.90, 8.66; See Appendix B for GC traces.



13

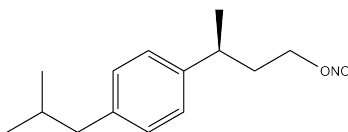
(R)-1-bromo-3-(4-isobutylphenyl)butan-2-ol (13) A 5 mL pear shaped flask equipped with a magnetic stir-bar was charged with alkene **3** (65.9 mg, 0.350 mmol) and 0.35 mL of dimethyl sulfoxide. To the stirred solution deionized water (0.01 mL, 0.7 mmol) was added as a single drop from a 21 gauge syringe needle and the flask was chilled on an ice bath until the solution had frozen. The ice bath was removed and once stirring had resumed N-bromosuccinimide (0.1235 g, 0.6939 mmol) was added in a single portion. The yellow solution was stirred for an additional two hours

then quenched with 0.5 mL of water and extracted with diethyl ether (4x 1.0 mL). The colorless ether extracts were dried over magnesium sulfate then purified *via* flash column chromatography (1:5 ethyl acetate: hexanes) to provide a crude mixture of two closely running spots as a pale yellow viscous oil (92.1 mg, 92.3%). The mixture was further purified *via* preparatory thin layer chromatography (1:5 ethyl acetate: hexanes) to isolate each spot as a crude mixture of multiple products. See Appendix A for ^1H NMR data of the crude products. See Appendix B for GC traces.



14

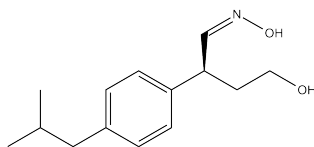
(S)-1-bromo-3-methyl-3-phenylpentan-2-ol (14) A 10 mL pear shaped flask equipped with a magnetic stir-bar was charged with alkene **4** (57.9 mg, 0.361 mmol) and 0.35 mL of dimethyl sulfoxide. To the stirred solution deionized water (0.01 mL, 0.7 mmol) was added as a single drop from a 21 gauge syringe needle and the flask was chilled on an ice bath until the solution had frozen. The ice bath was removed and once stirring had resumed N-bromosuccinimide (0.1262 g, 0.7090 mmol) was added in a single portion. The yellow solution was stirred for 3.5 hours then quenched with 0.5 mL of water and extracted with diethyl ether (4x 1.5 mL). The ether was dried over magnesium sulfate and purified *via* flash column chromatography (1:5 ethyl acetate: hexanes) to afford a crude mixture of products as a colorless cloudy oil (83.1 mg, 89.4%). The mixture was further purified *via* preparatory thin layer chromatography (1:5 ethyl acetate: hexanes) to isolate two major spots as crude mixtures of multiple products. See Appendix A for ^1H NMR data of the crude products.



15

(S)-3-(4-isobutylphenyl)butyl nitrite (15) A 25 mL 3-neck round bottom flask equipped with a magnetic stir-bar, gas-inlet, pressure equalizing addition funnel topped with a rubber septum, and temperature probe was flame dried under vacuum, purged with nitrogen, then charged with

oven dried sodium carbonate (0.1549 g, 1.461 mmol) and alcohol **9** (0.2004 g, 0.9713 mmol) which was rinsed into the flask with 3 mL of acetonitrile. The stirred solution was chilled to -10°C using an acetone-ice bath and a solution of nitrosonium tetrafluoroborate (0.1962 g, 1.680 mmol) in 1.5 mL of acetonitrile was added dropwise through the funnel followed by a 0.5 mL rinse. The solution was stirred for 10 minutes and an additional portion of nitrosonium tetrafluoroborate (0.1573 g, 1.347 mmol) was added in a single portion as the solid. After 6 hours at room temperature the solution was poured into 20 mL of water and extracted with dichloromethane (4x 15 mL). The organic extracts were dried over magnesium sulfate and concentrated *in vacuo* to provide a crude yellow liquid (0.2085 g, 91.17%). The crude product was purified by Kugelrohr distillation to yield nitrite **15** as a yellow liquid (0.1554 g, 67.95%). R_f 0.65 (1:3 ethyl acetate: hexanes); ^1H NMR (250 MHz, CDCl_3) δ_H 7.13-7.05 (m, 4H), 4.68-4.46 (m, 2H), 2.82 (sext, 1H, J 7.2 Hz), 2.44 (d, 2H, J 7 Hz), 2.00 (q, 2H, J 7 Hz), 1.93-1.79 (m, 1H), 1.29 (d, 3H, J 6.8 Hz), 0.90 (d, 6H, J 6.8 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ_C 143.13, 139.84, 129.42, 126.75, 61.51, 45.17, 37.34, 36.18, 30.36, 22.54, 22.45; IR (neat) 1647 cm^{-1} (strong), 1604 cm^{-1} (strong).



16

(S)-4-hydroxy-2-(4-isobutylphenyl)butanal oxime (16) A 25 mL 3-neck round bottom flask equipped with a magnetic stir-bar, flow controlled gas inlet, air condenser topped with a rubber septum, and glass stopper was flame dried under vacuum, purged with dry nitrogen, and charged with nitrite **15** (49.5 mg, 0.210 mmol) in a colorless solution of 6.25 mL of still dried benzene. A syringe was inserted through the rubber septum and approximately 60 mL of the atmosphere was withdrawn. The flow controlled gas inlet was closed and the entire apparatus was placed in a medium pressure photochemical reactor. After 3 hours the yellow solution was concentrated *in vacuo* to afford a crude dark orange oil tentatively identified as oxime **16**. See Appendix A for ^1H and ^{13}C NMR spectra of the crude compound. IR (CCl_4) 3389 cm^{-1} (broad), 1633 cm^{-1} (weak).

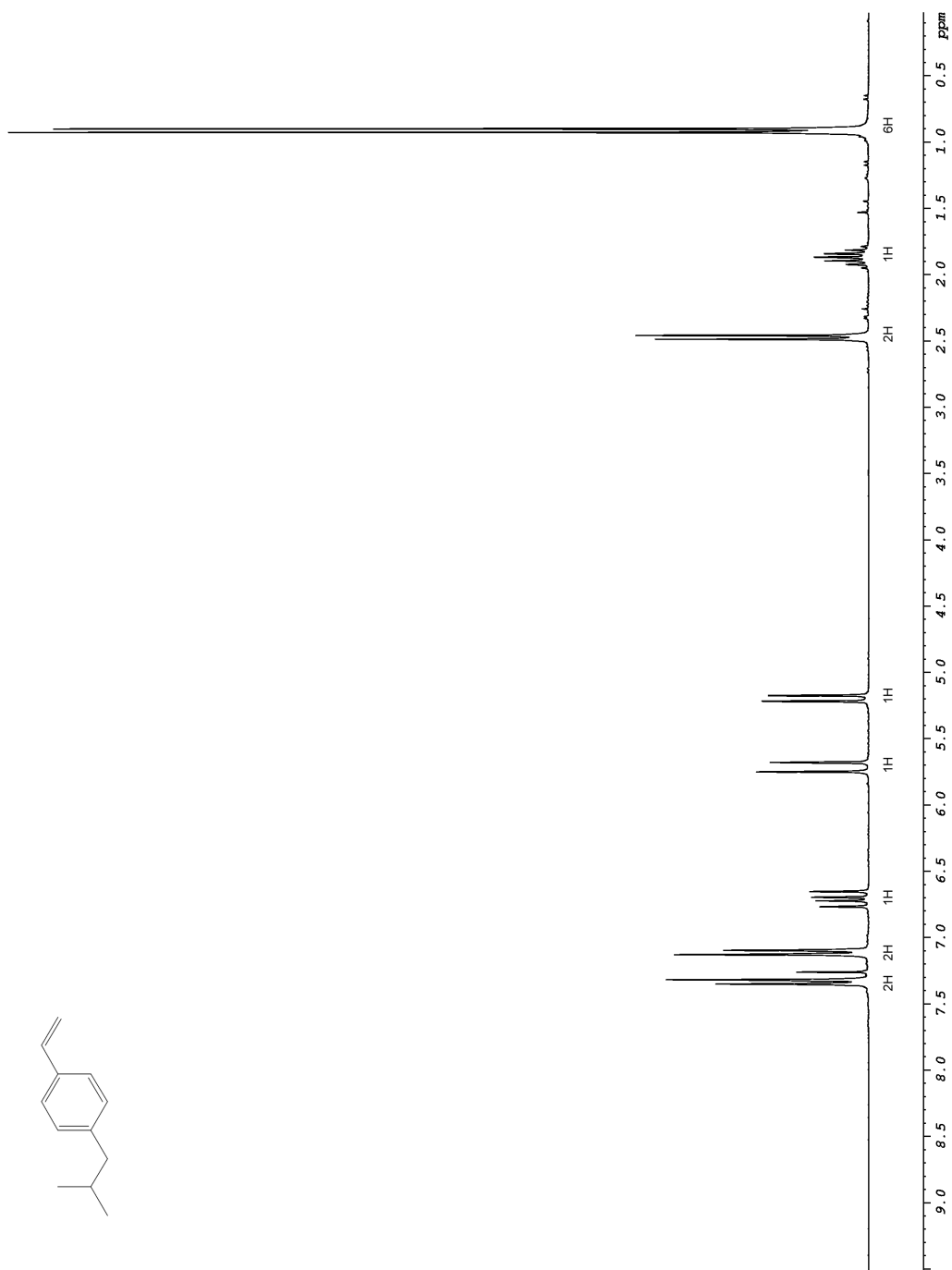
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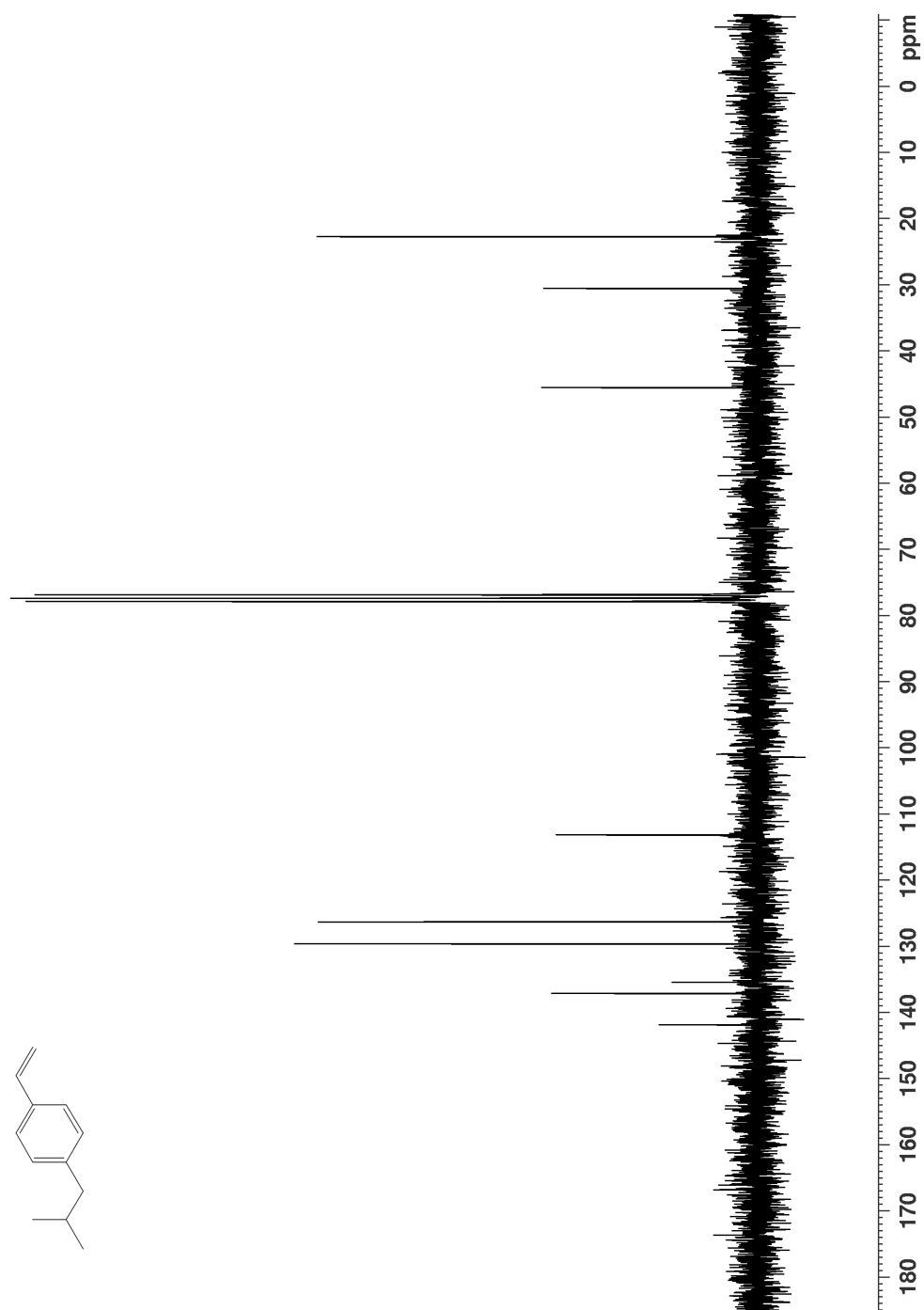
6 Appendix

6.1 Appendix A, ^1H and ^{13}C NMR Spectra

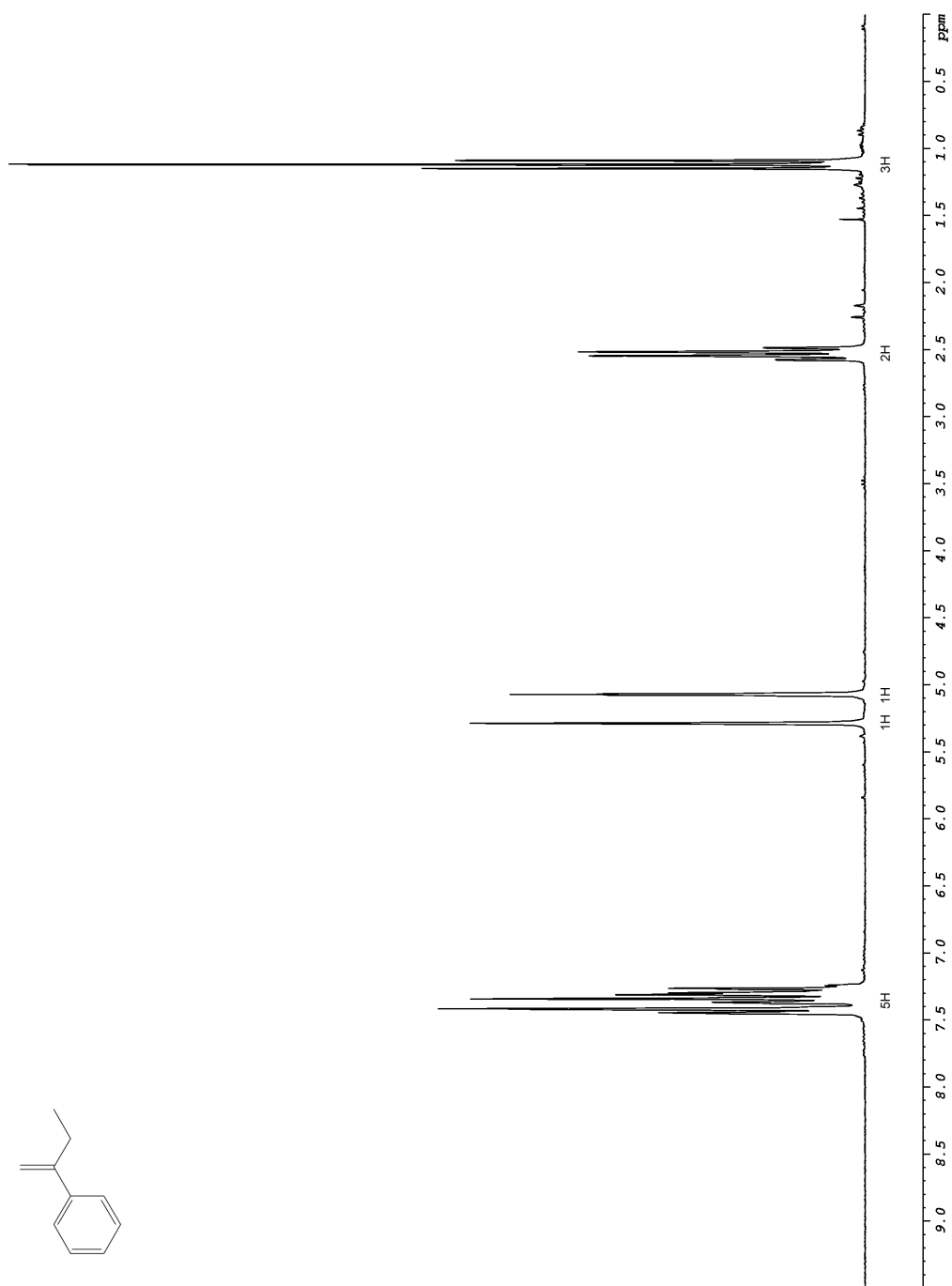
Alkene **1** ^1H NMR, 250 MHz, CDCl_3



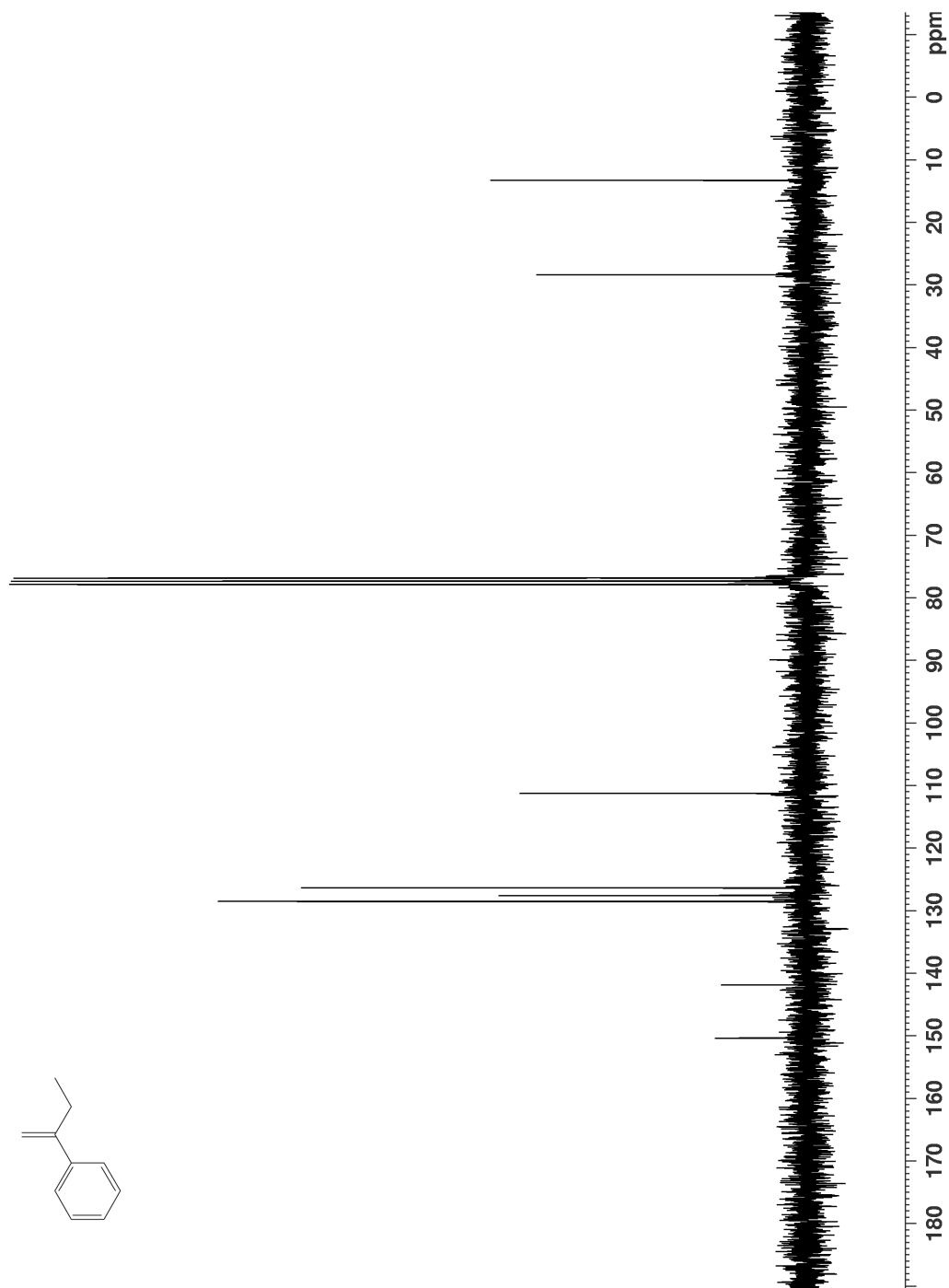
Alkene **1** ^{13}C NMR, 62.9 MHz, CDCl_3



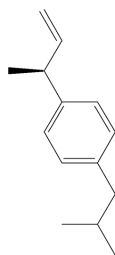
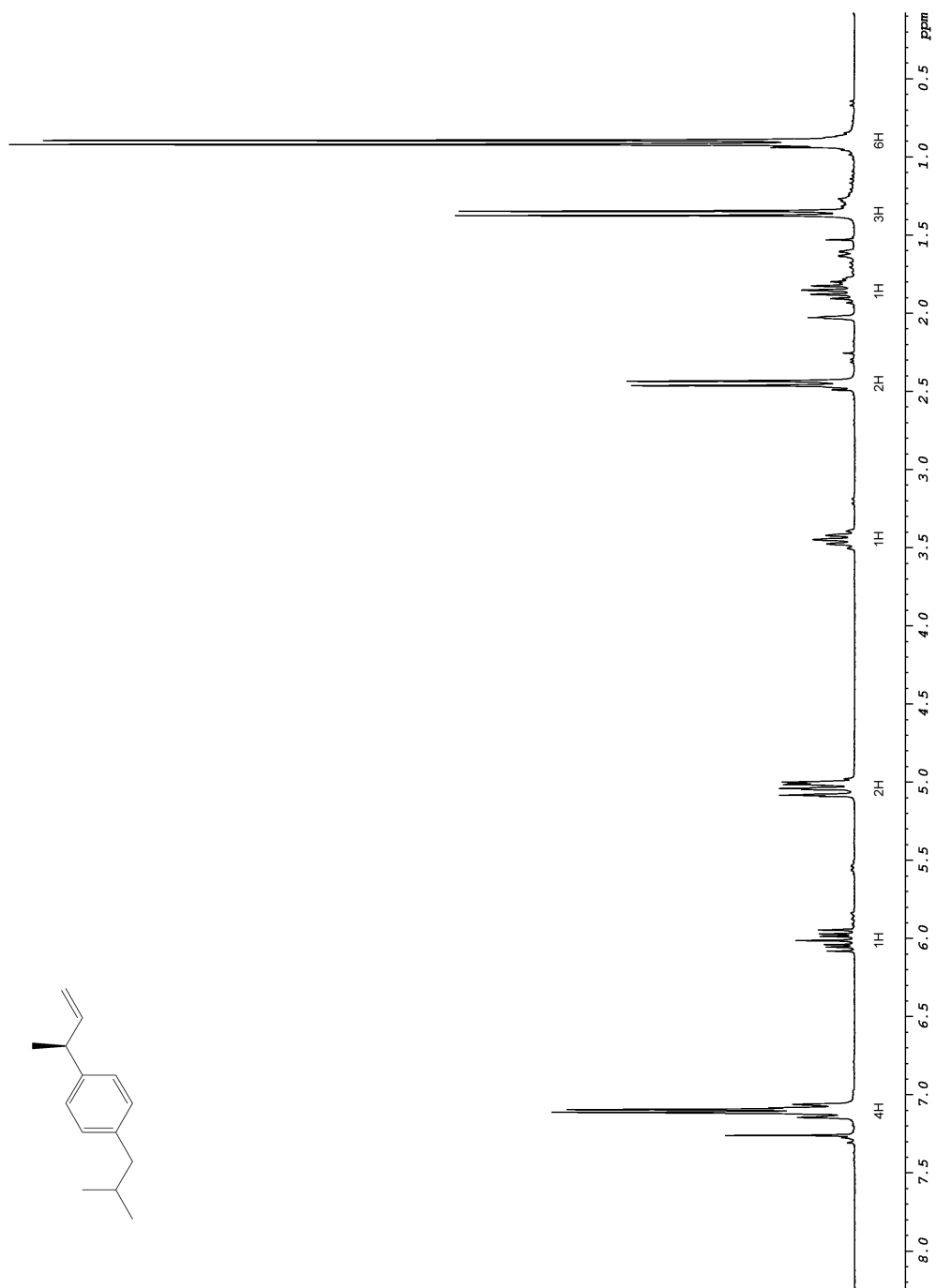
Alkene **2** ^1H NMR, 250 MHz, CDCl_3



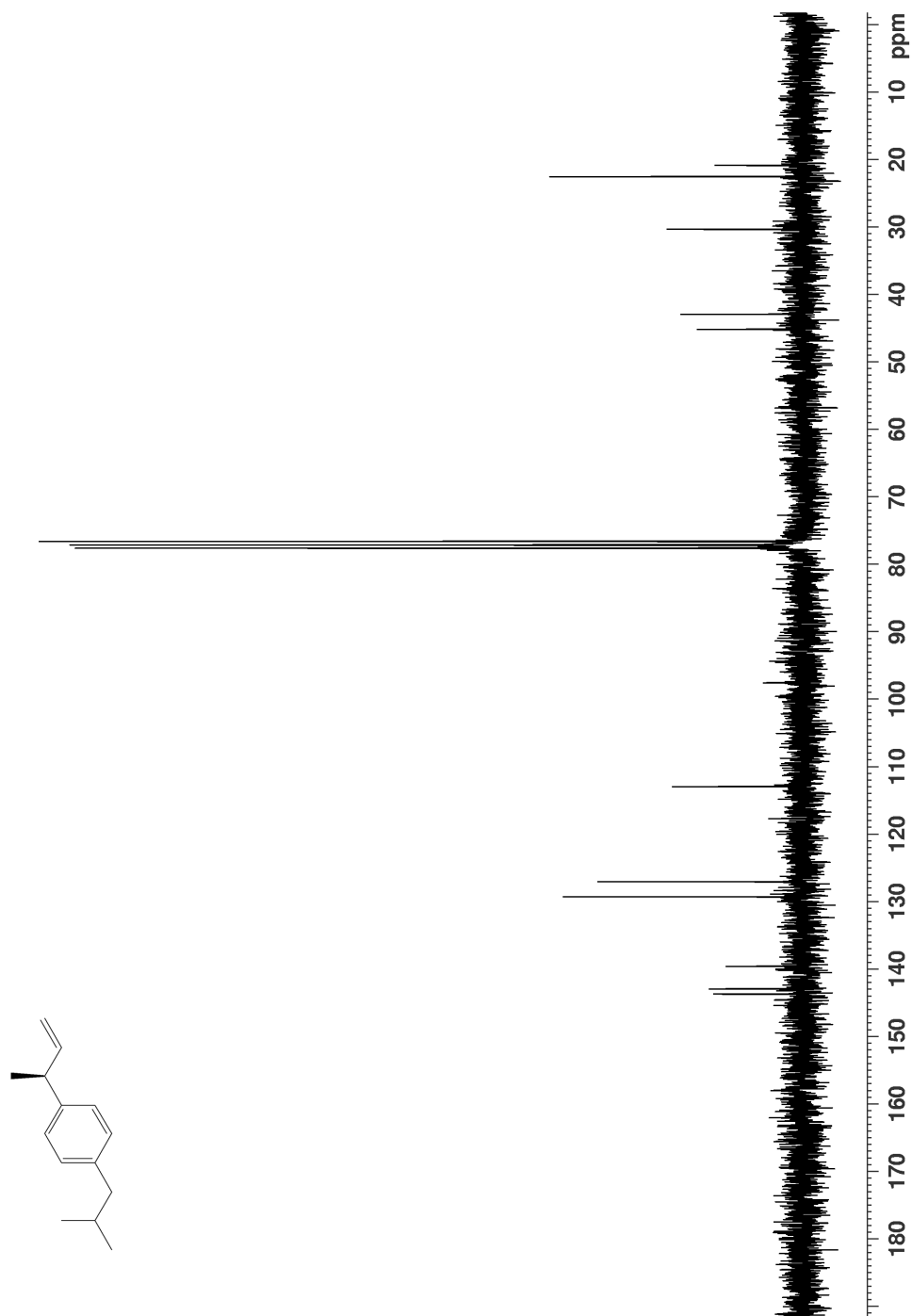
Alkene **2** ^{13}C NMR, 62.9 MHz, CDCl_3



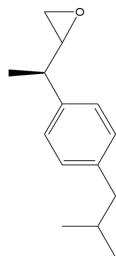
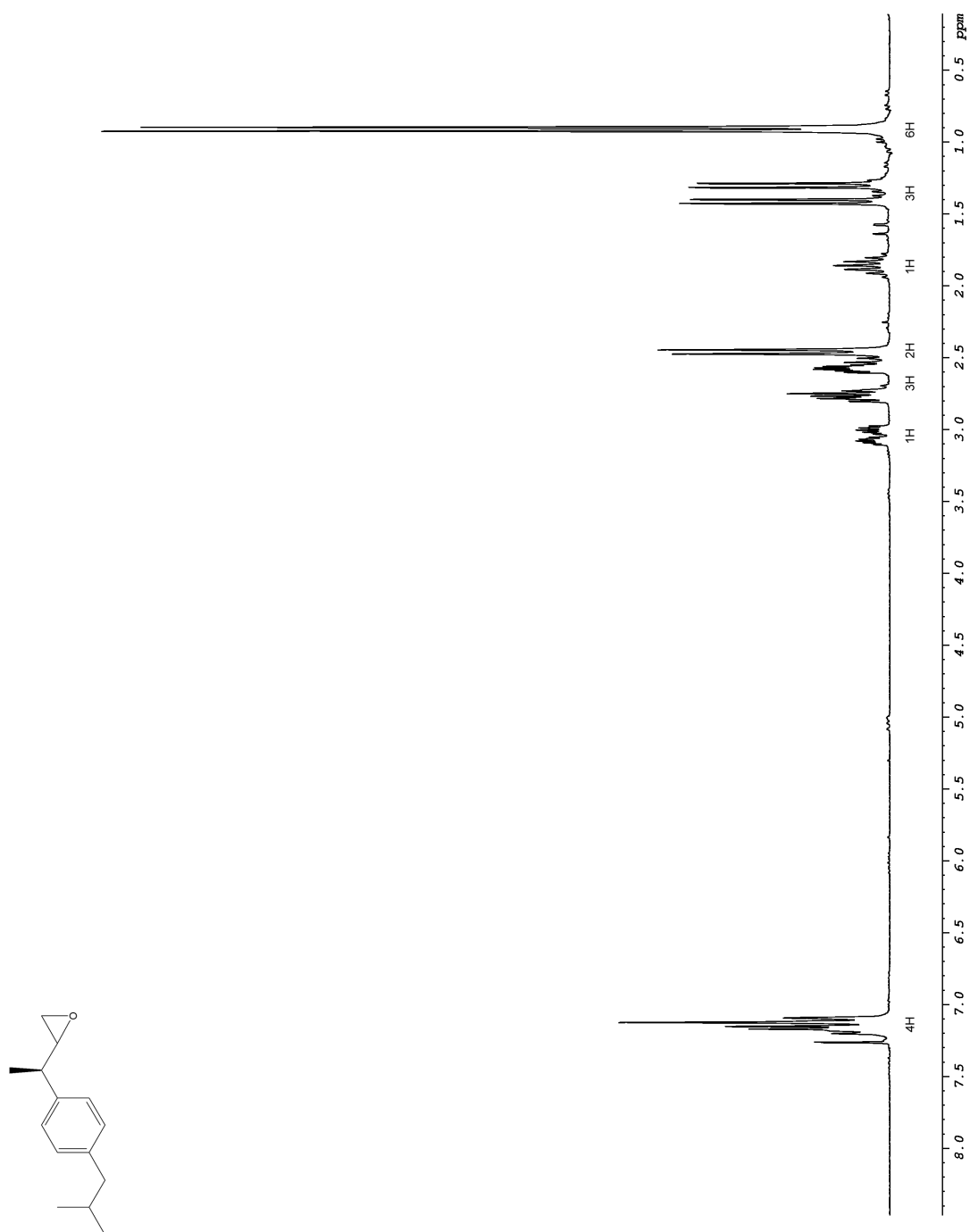
Alkene **3** ^1H NMR, 250 MHz, CDCl_3



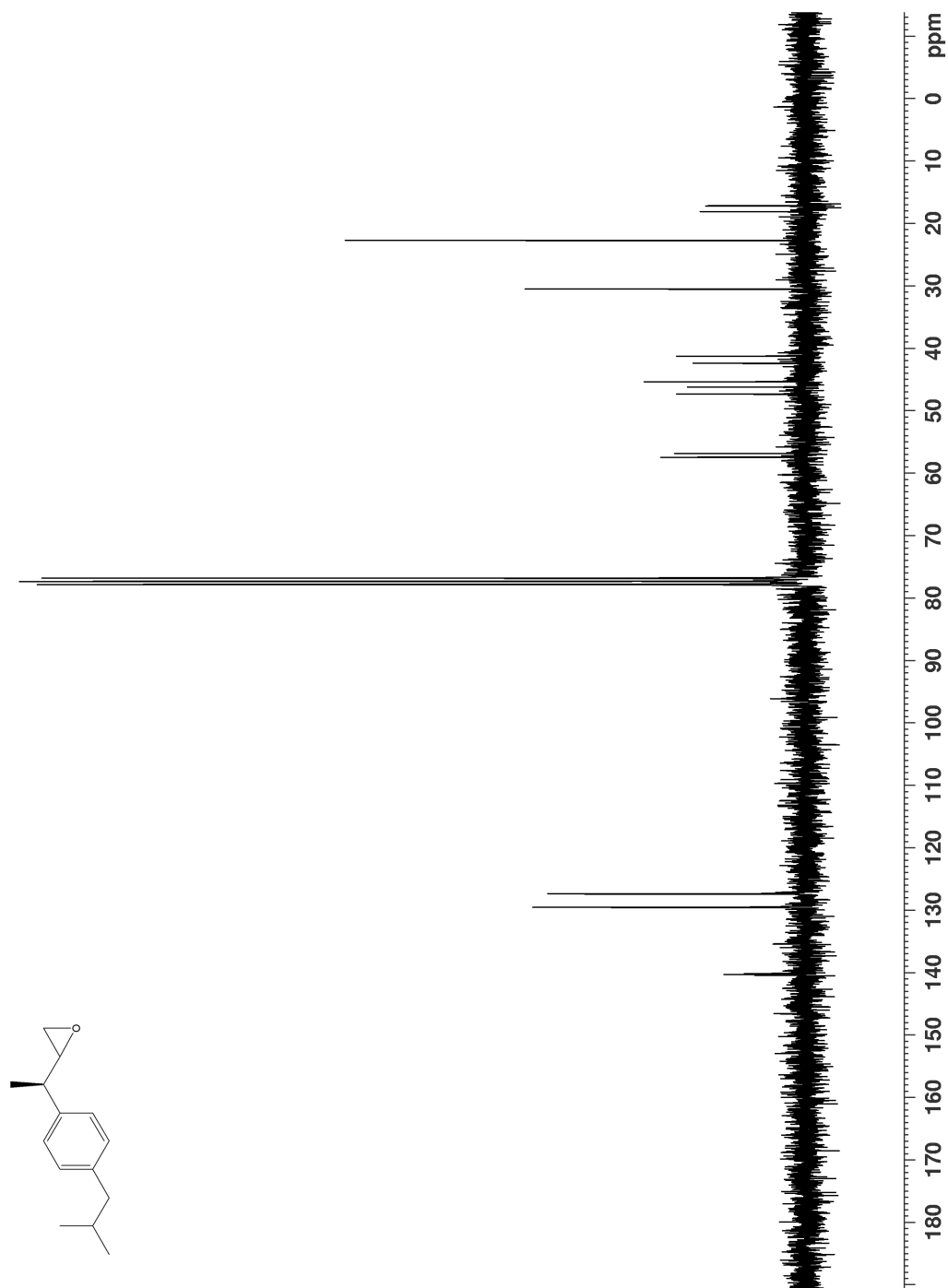
Alkene **3** ^{13}C NMR, 62.9 MHz, CDCl_3



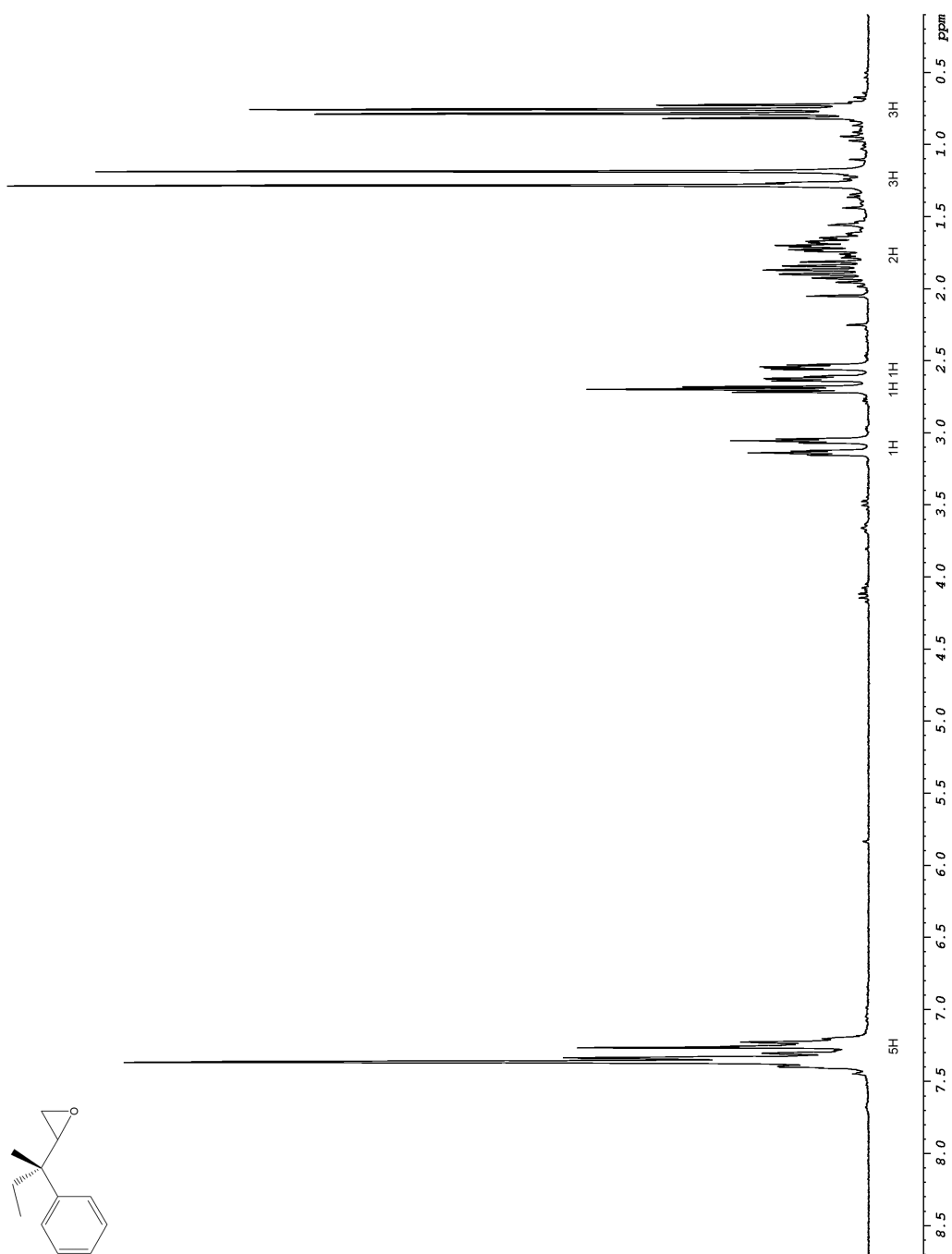
Epoxide **5** ^1H NMR, 250 MHz, CDCl_3



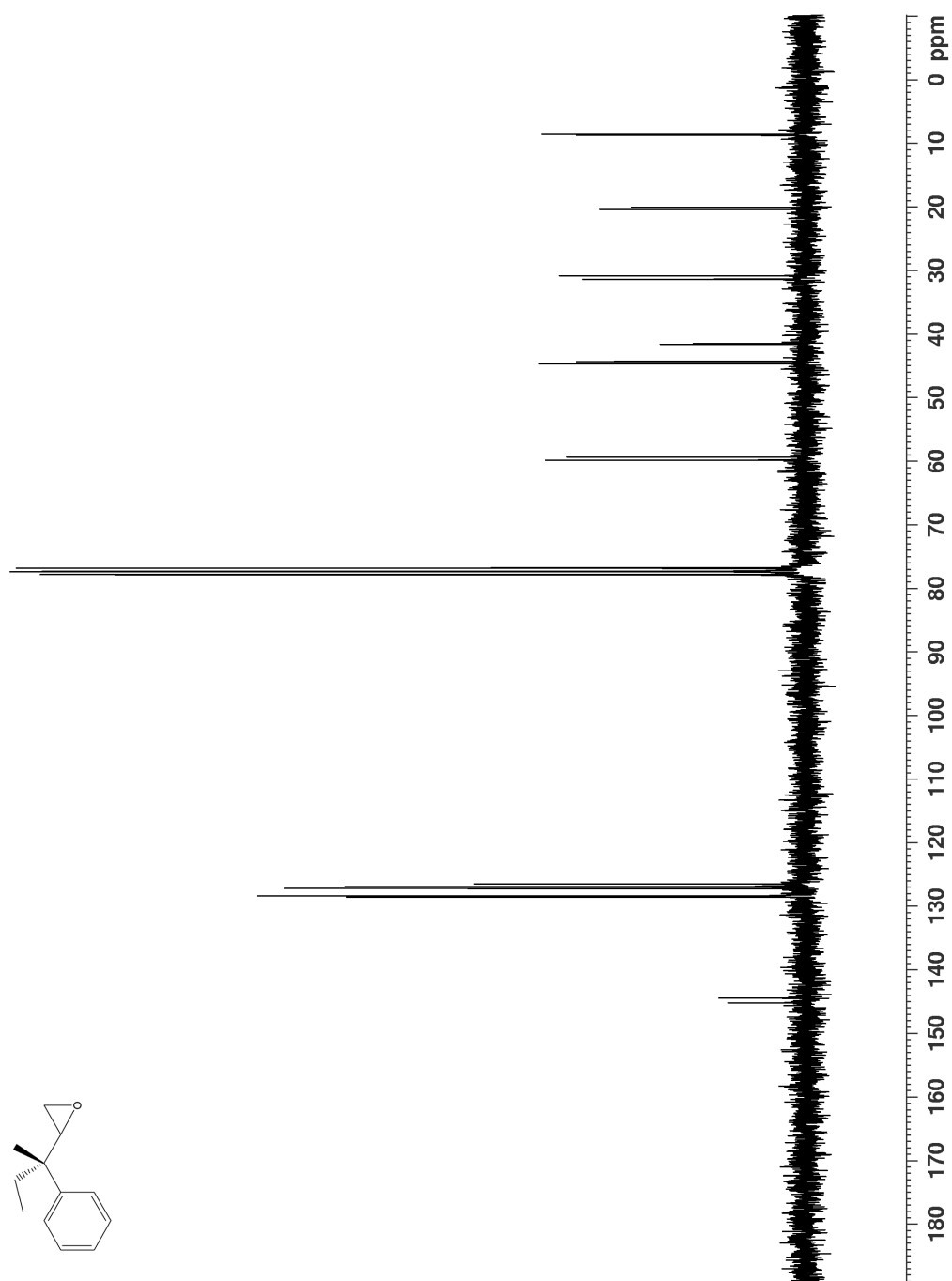
Epoxide **5** ^{13}C NMR, 62.9 MHz, CDCl_3



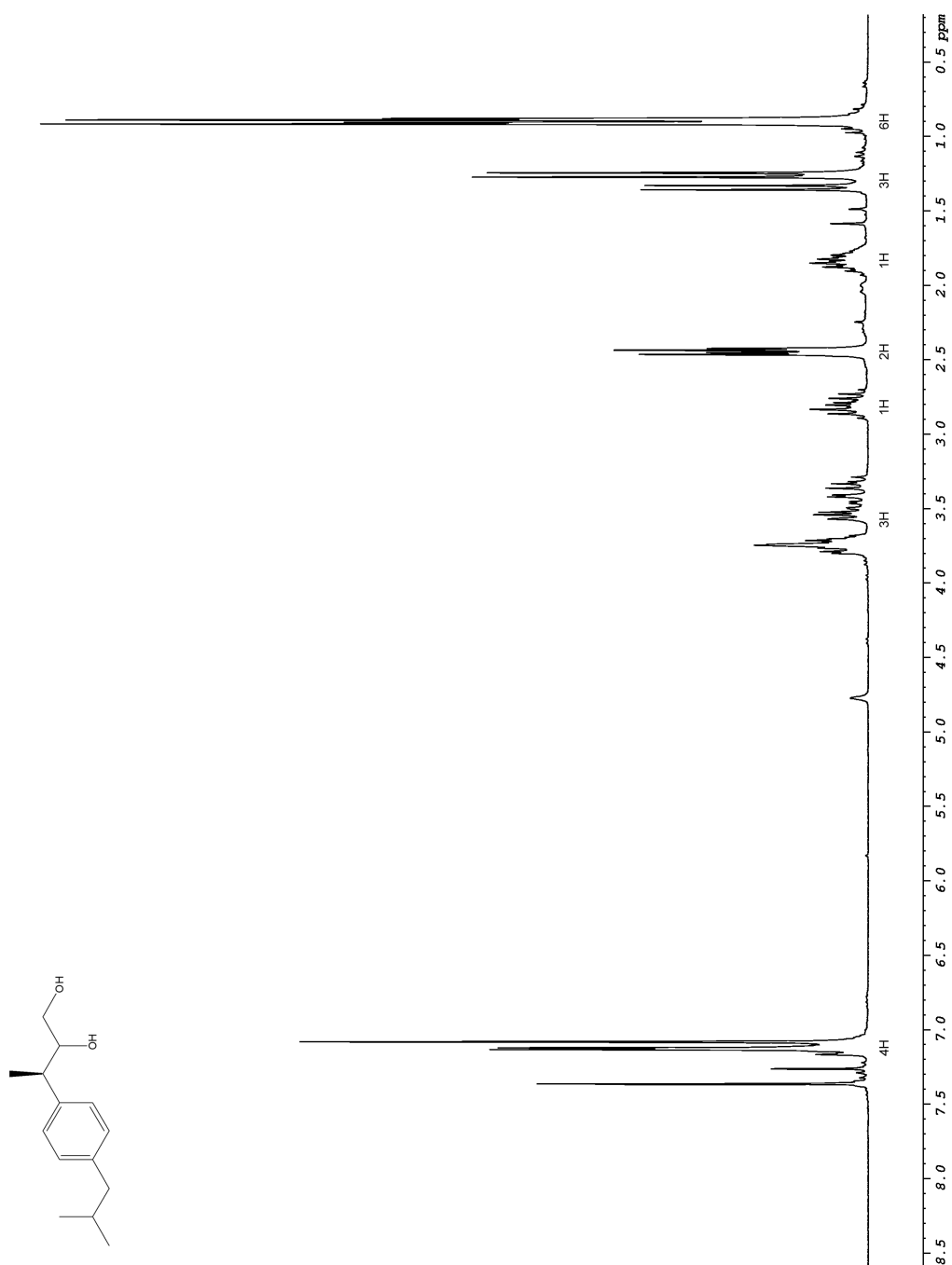
Epoxide **6** ¹H NMR, 250 MHz, CDCl₃



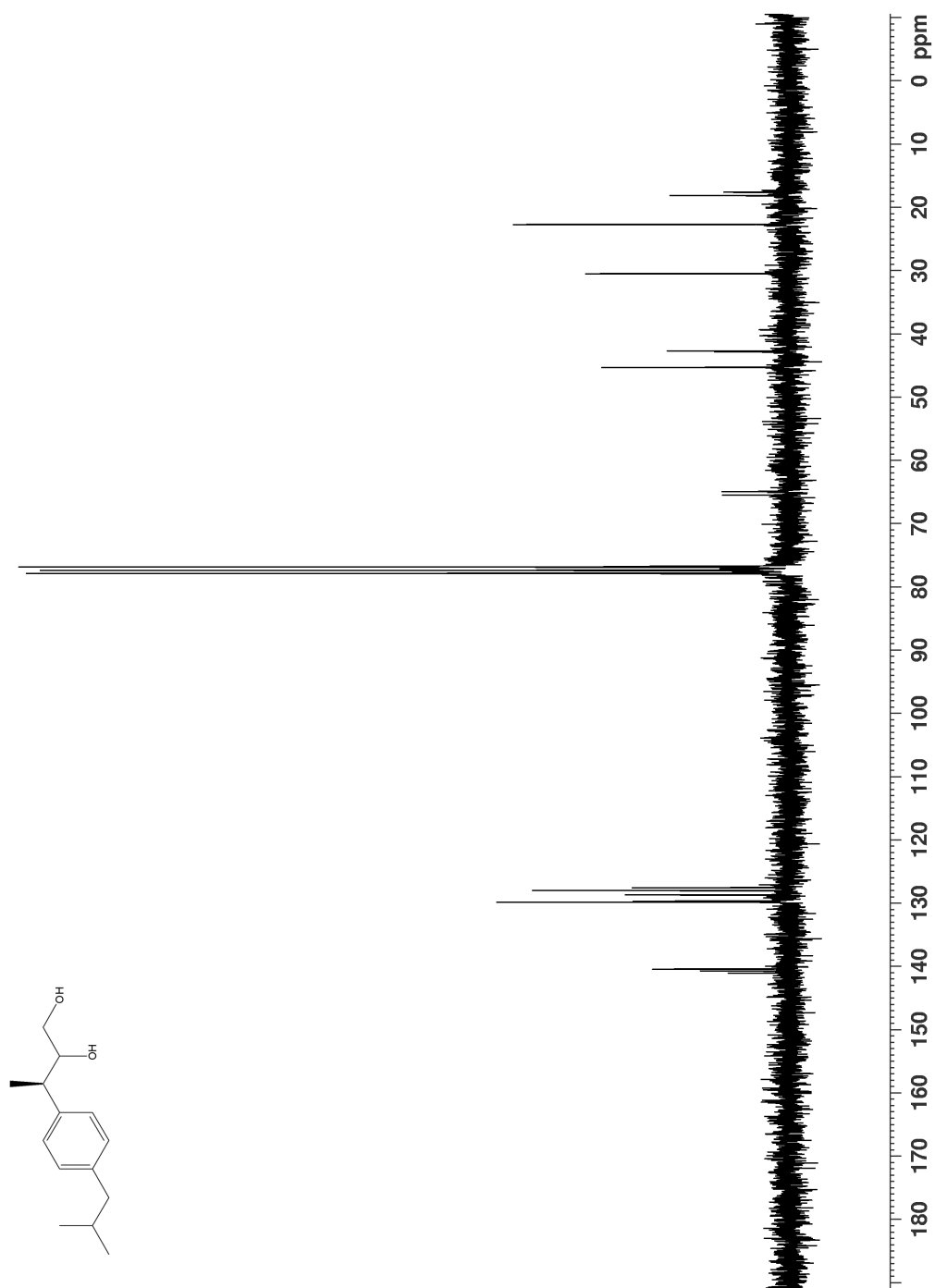
Epoxide **6** ^{13}C NMR, 62.9 MHz, CDCl_3



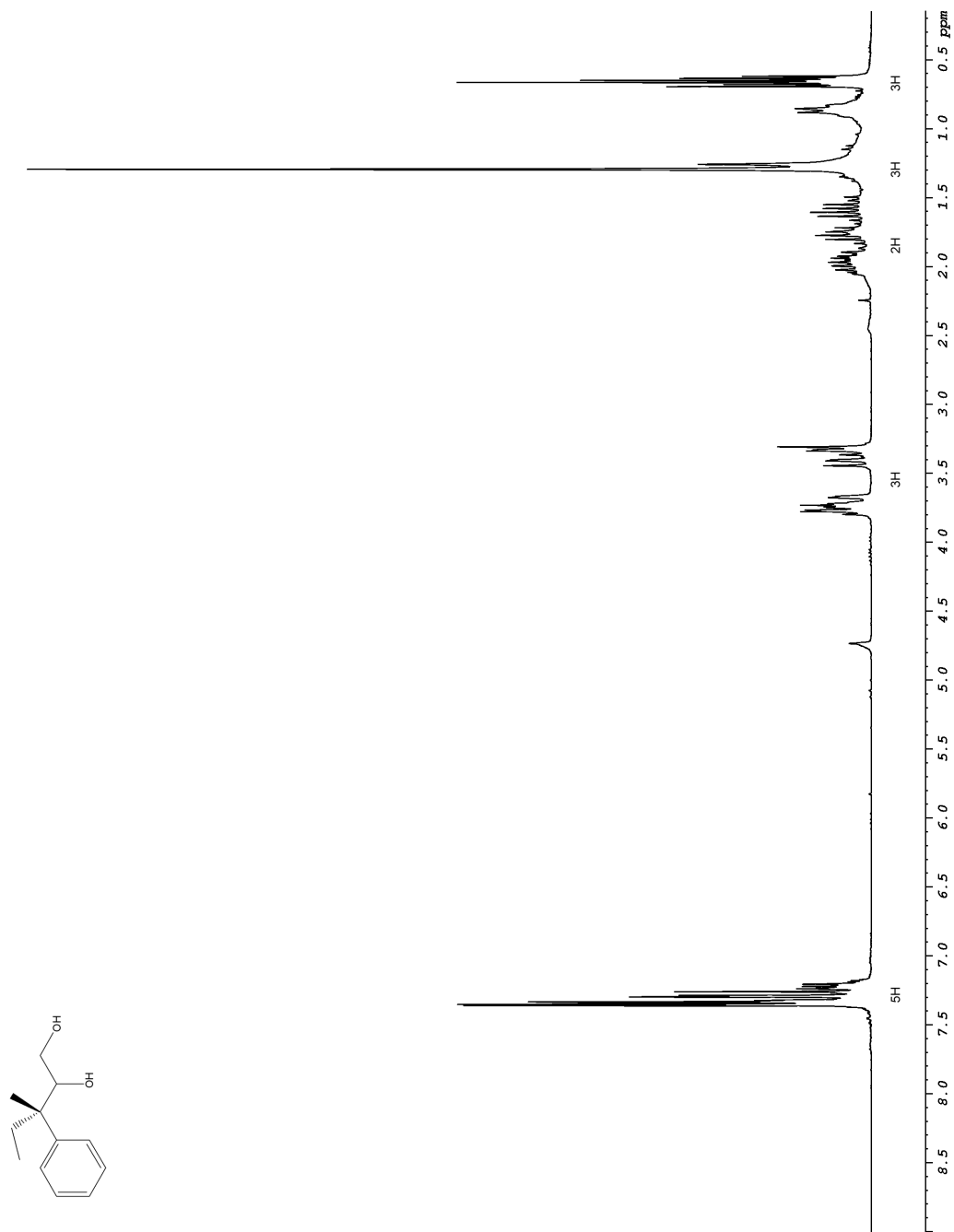
Diol **7** ^1H NMR, 250 MHz, CDCl_3 / D_2O
Benzene contamination seen at $\delta = 7.36$.



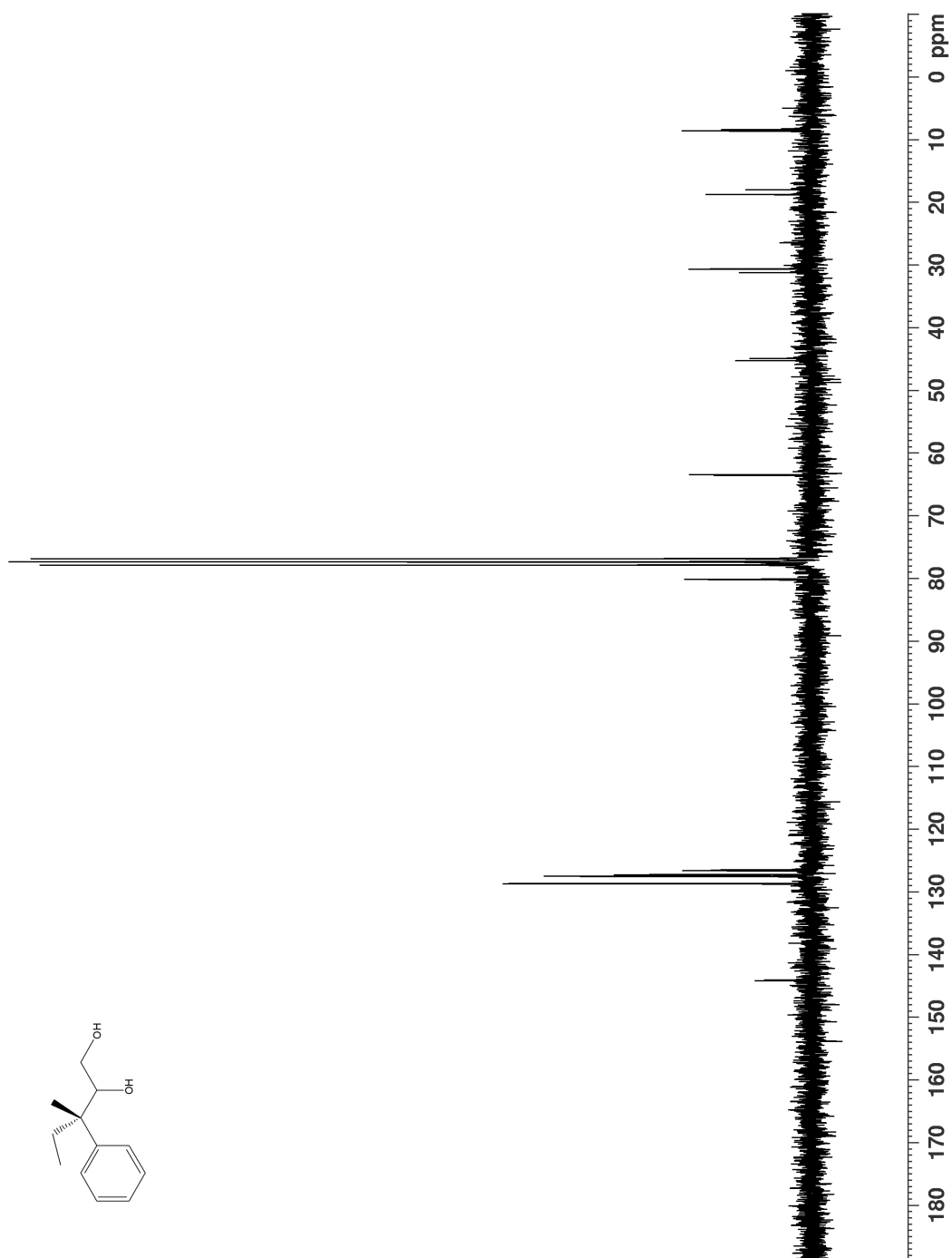
Diol **7** ^{13}C NMR, 62.9 MHz, CDCl_3



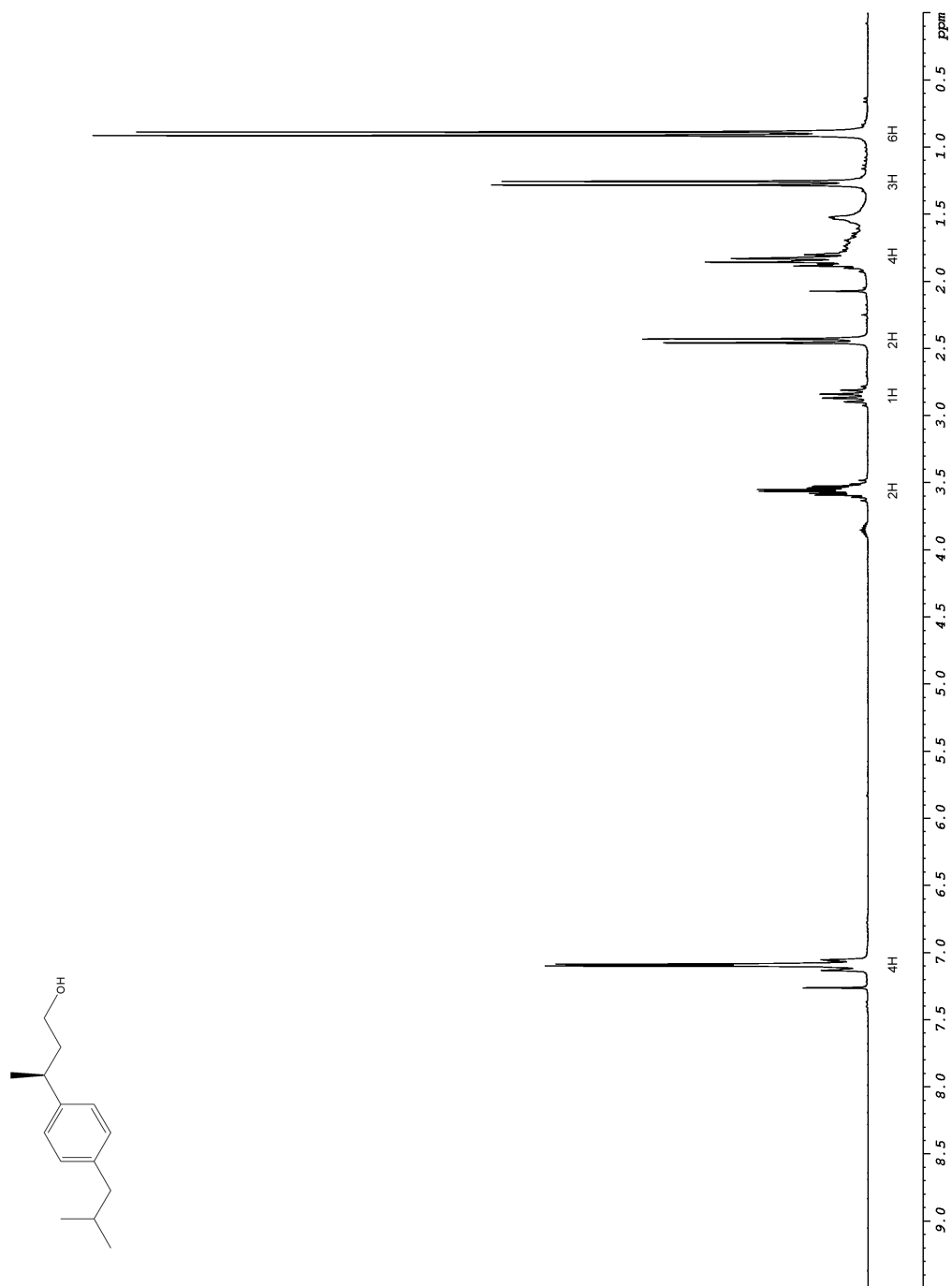
Diol **8** ^1H NMR, 250 MHz, CDCl_3 / D_2O
Benzene contamination at $\delta = 7.36$.



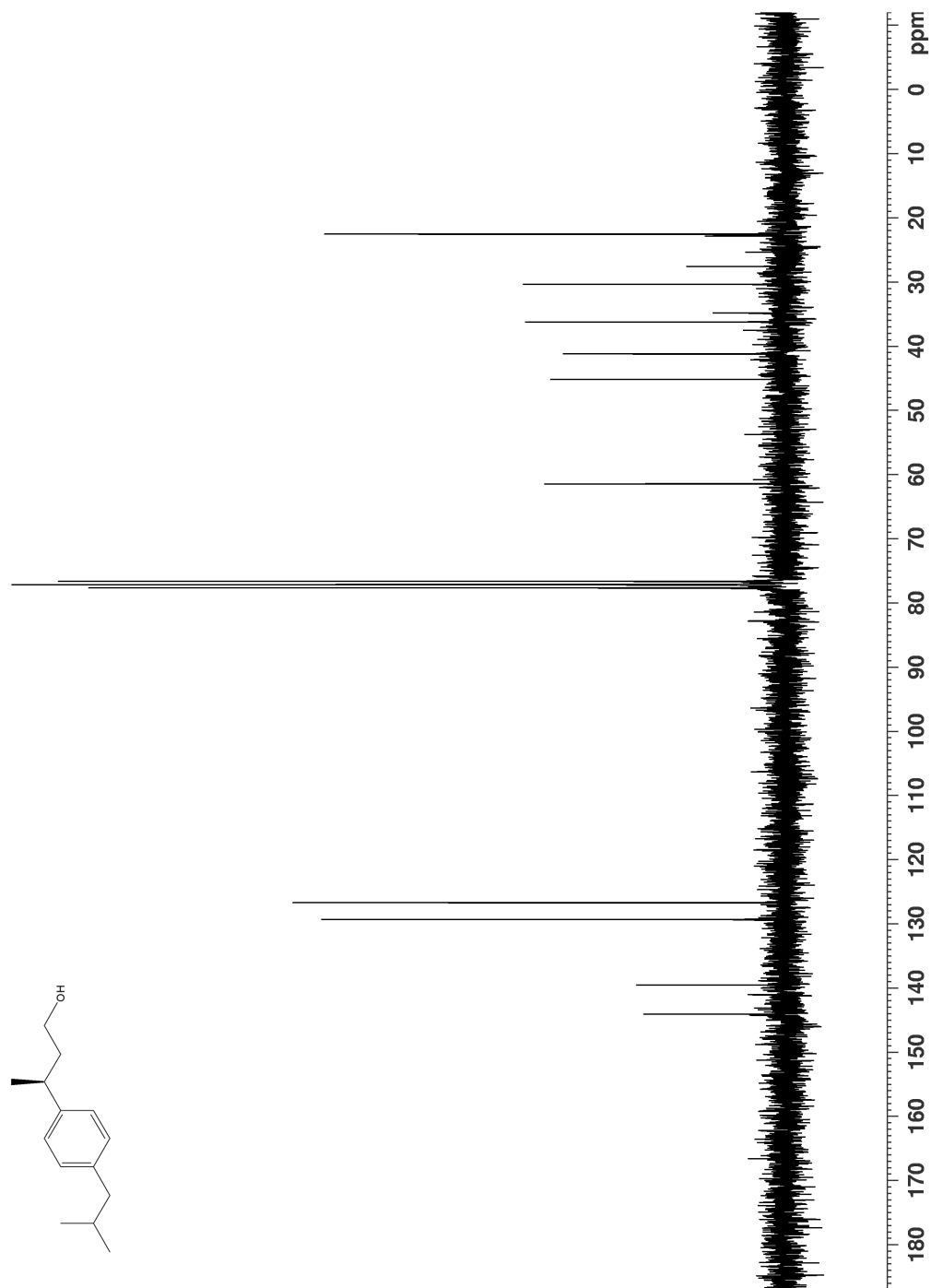
Diol **8** ^{13}C NMR, 62.9 MHz, CDCl_3



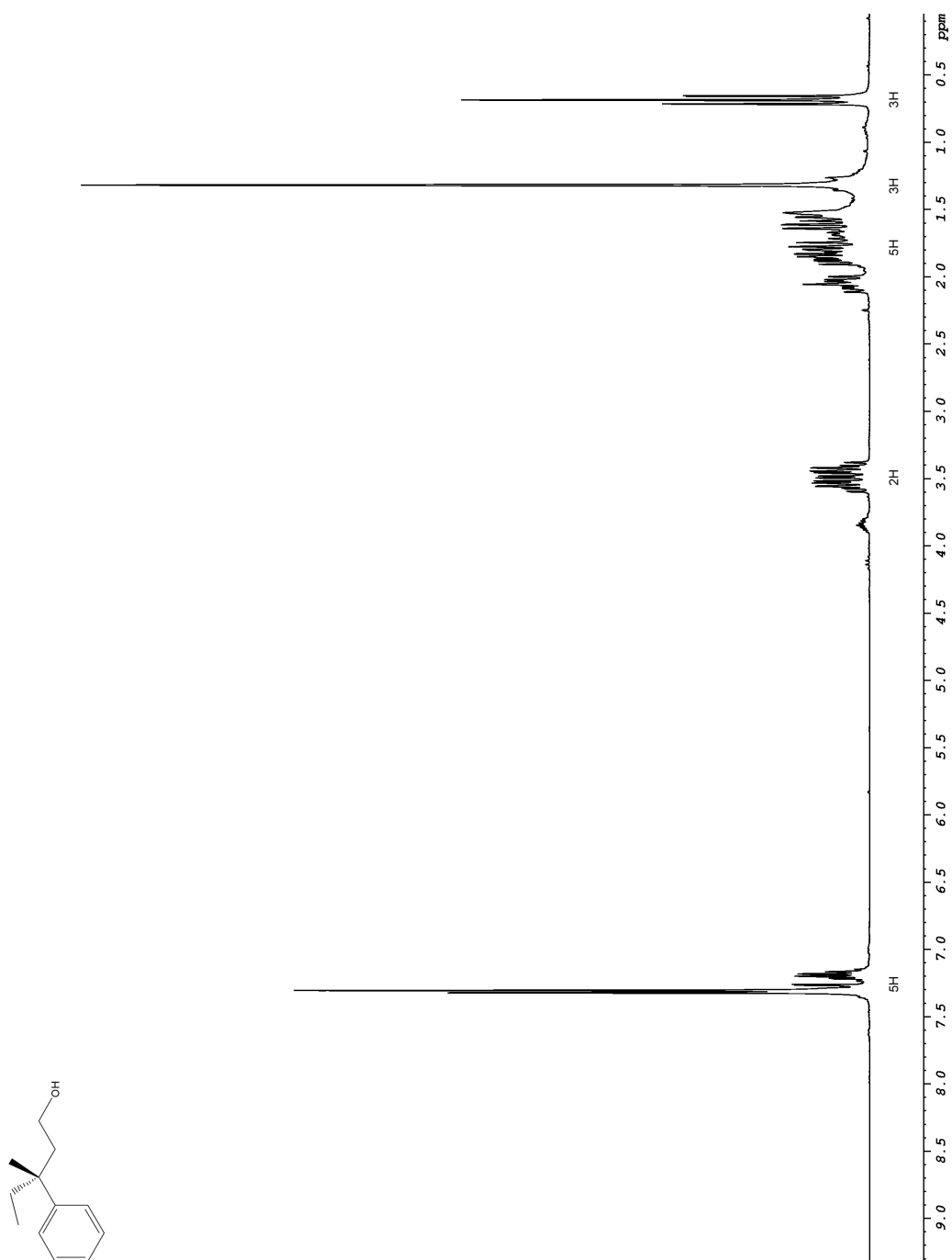
Alcohol **9** ^1H NMR, 250 MHz, CDCl_3



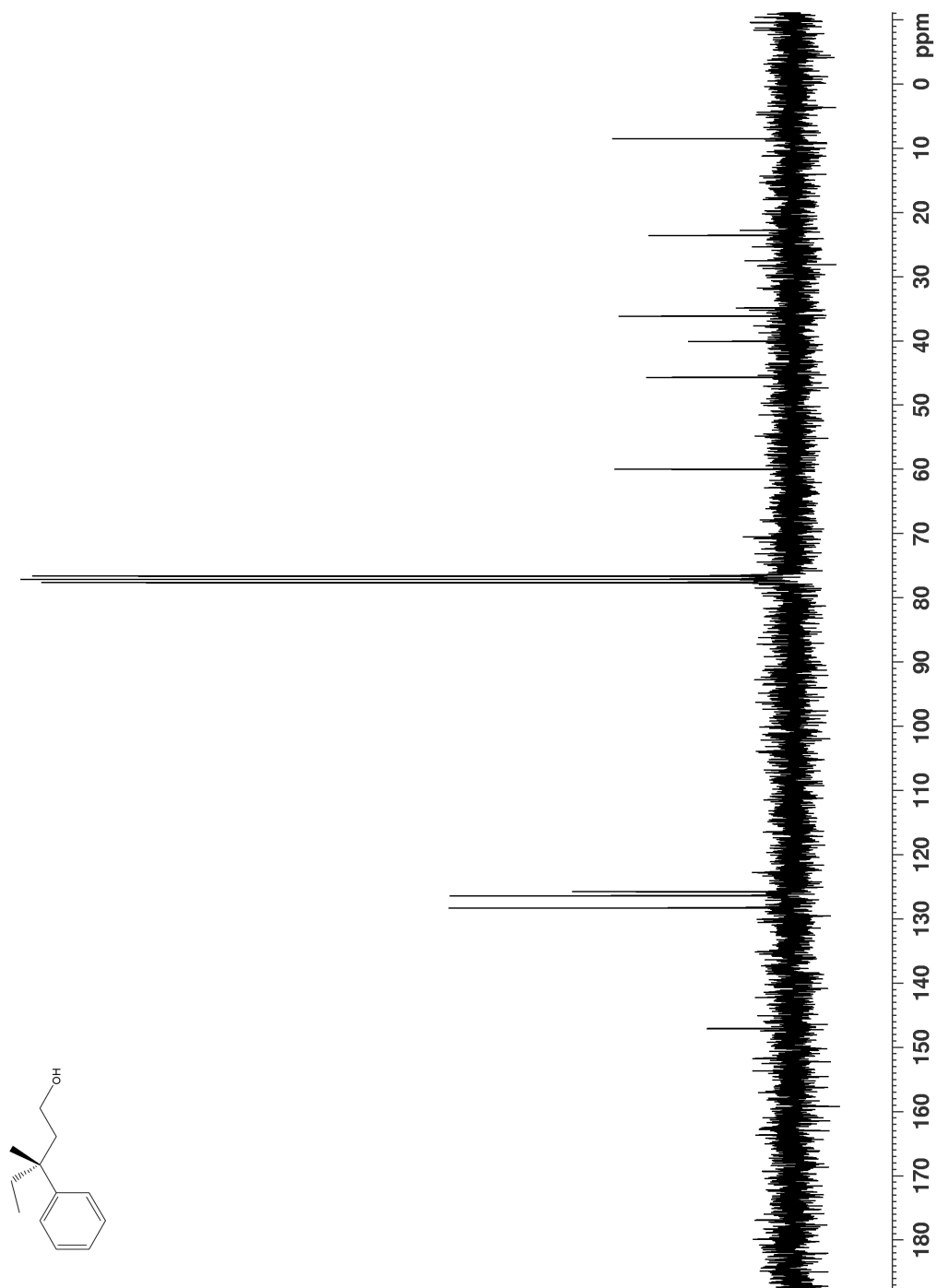
Alcohol **9** ^{13}C NMR, 62.9 MHz, CDCl_3



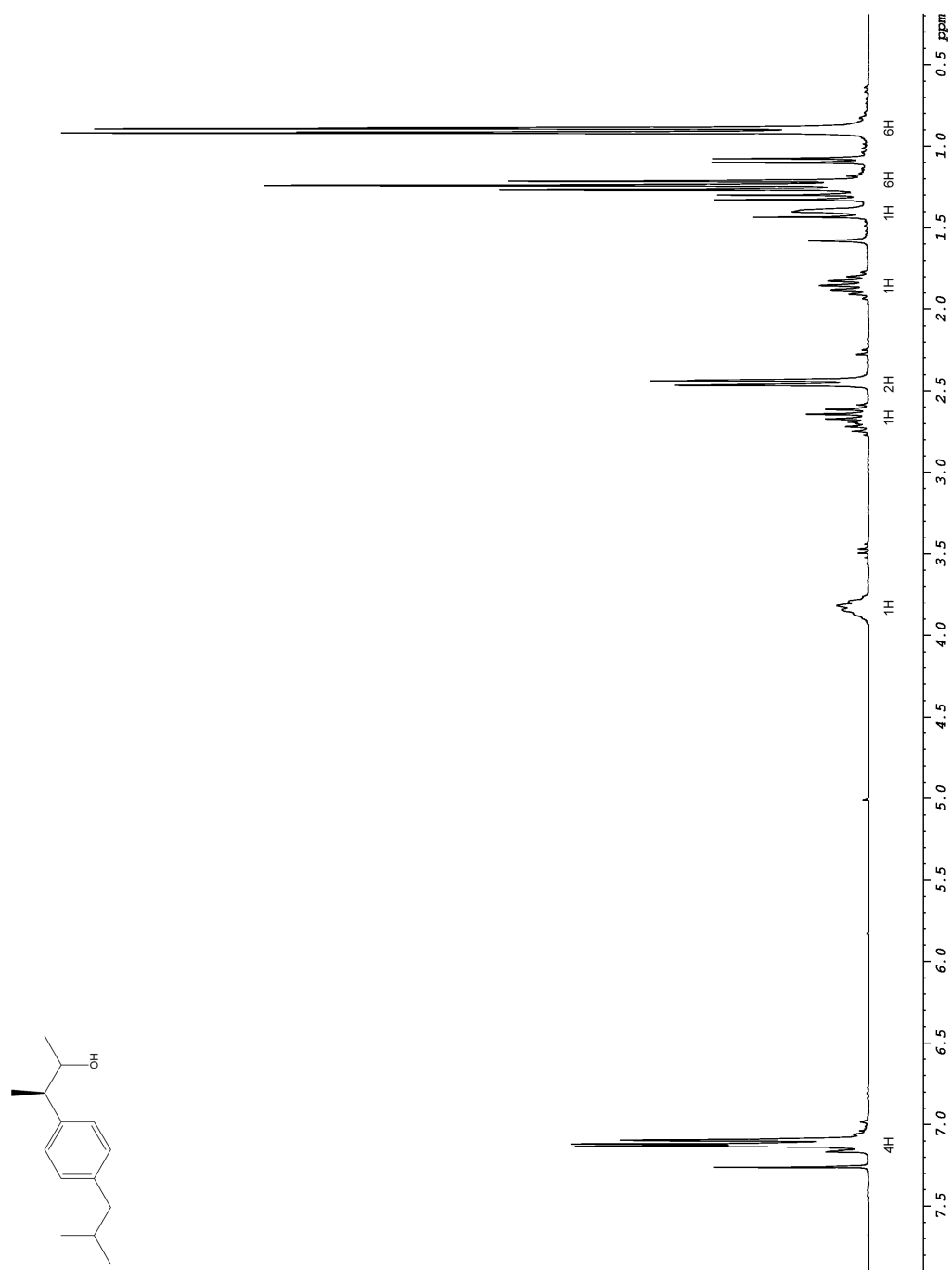
Alcohol **10** ^1H NMR, 250 MHz, CDCl_3



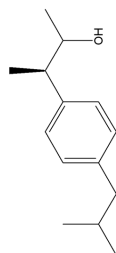
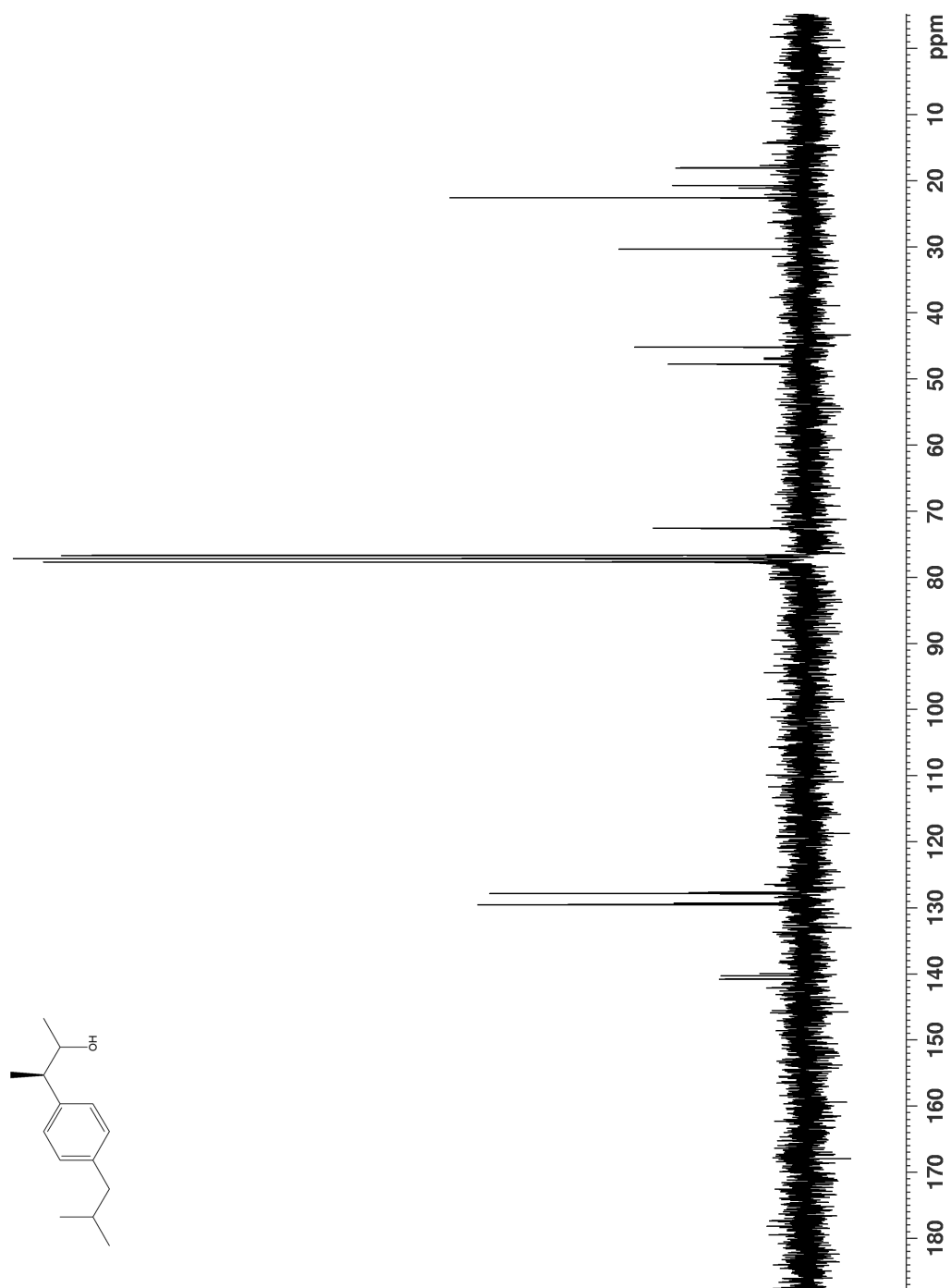
Alcohol **10** ^{13}C NMR, 62.9 MHz, CDCl_3



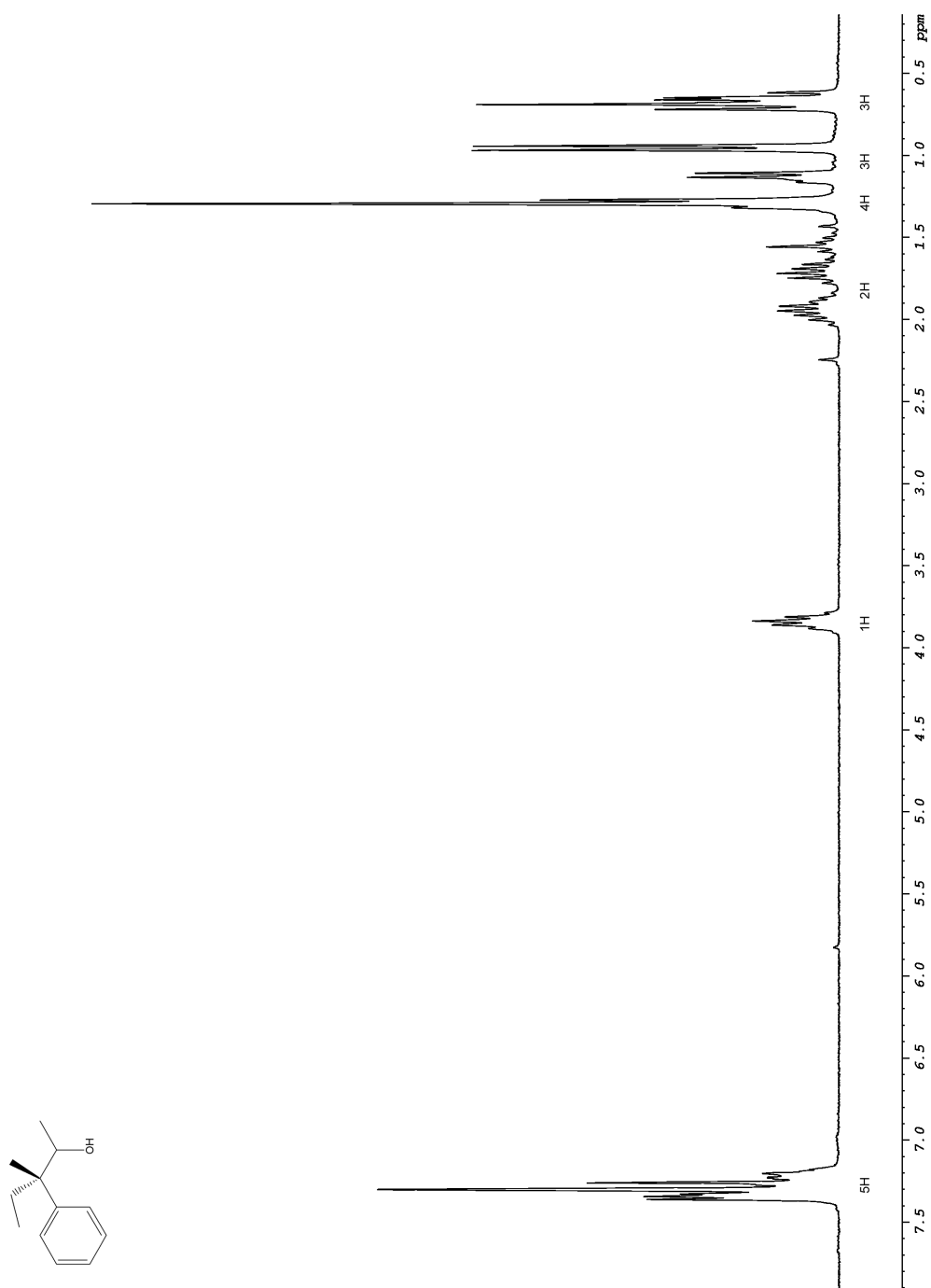
Alcohol **11** ^1H NMR, 250 MHz, CDCl_3



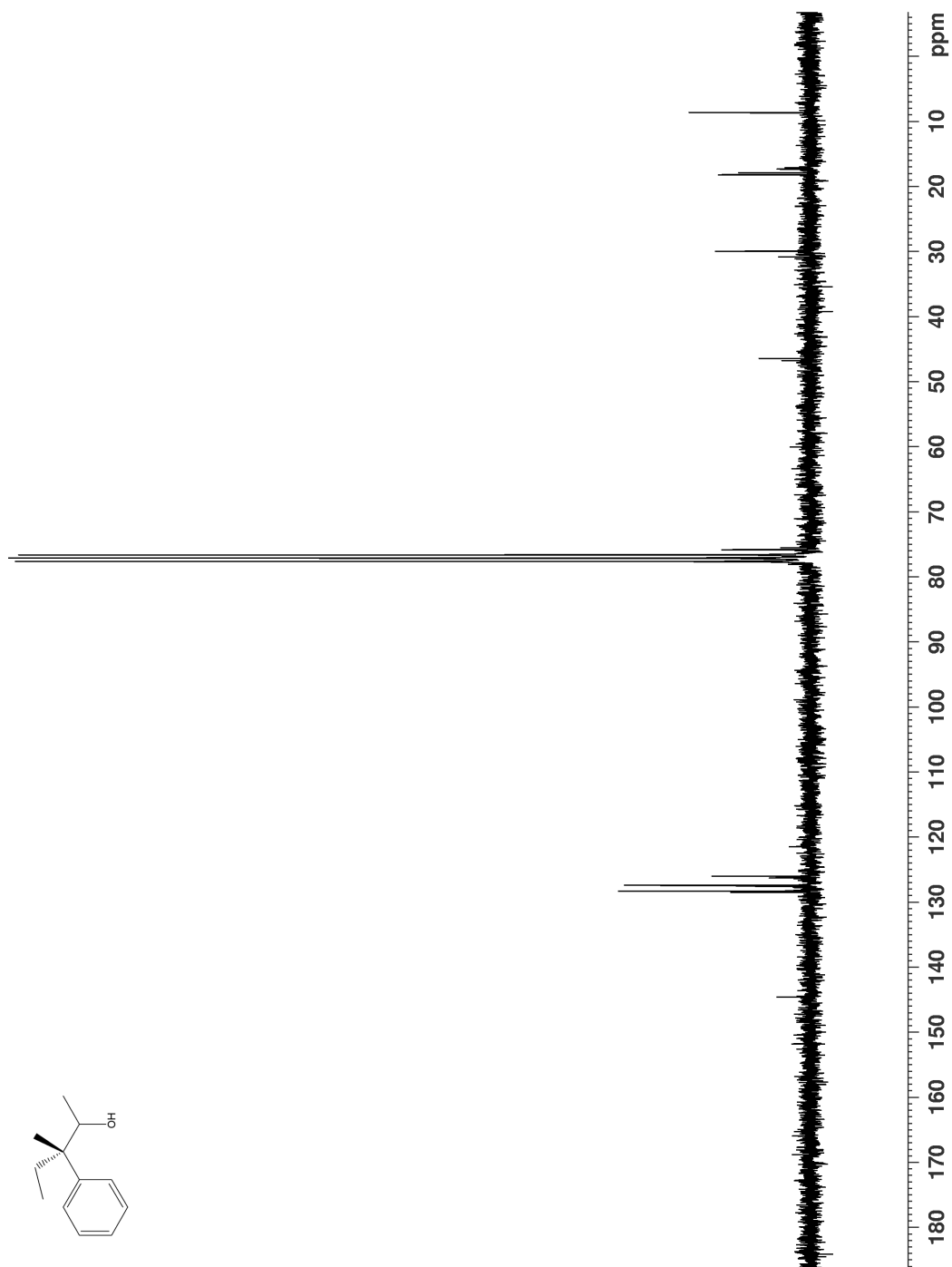
Alcohol **11** ^{13}C NMR, 62.9 MHz, CDCl_3



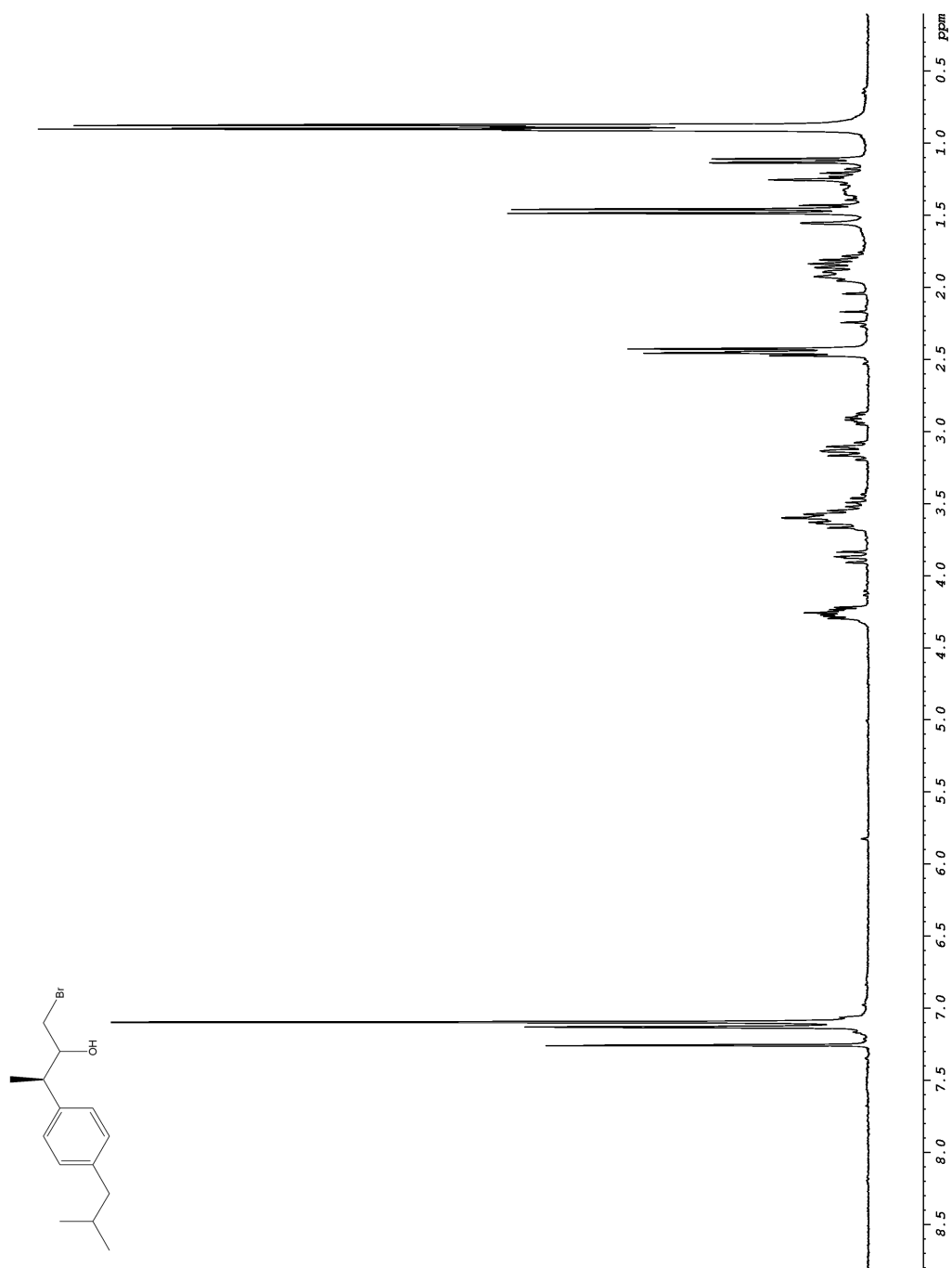
Alcohol **12** ^1H NMR, 250 MHz, CDCl_3



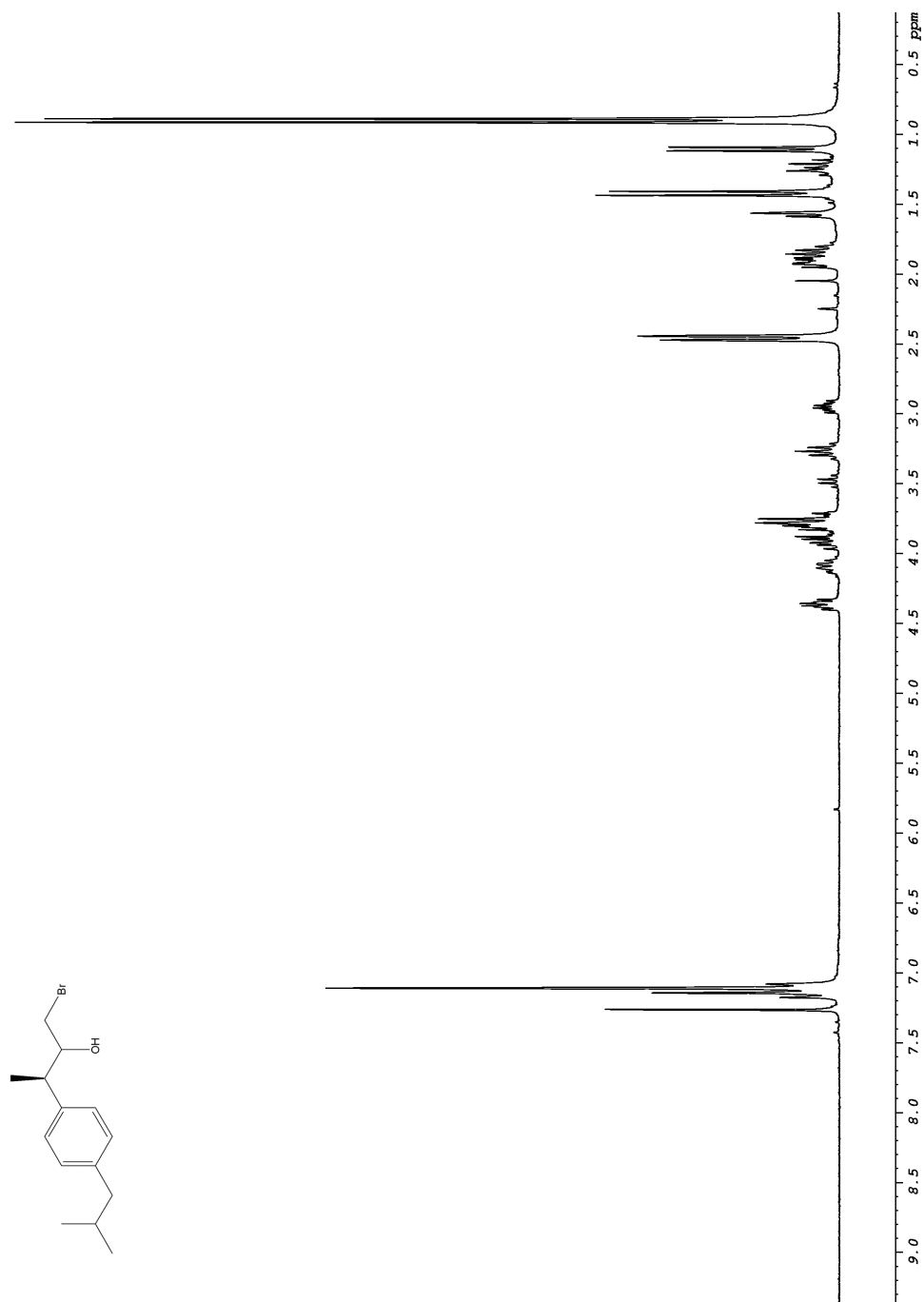
Alcohol **12** ^{13}C NMR, 62.9 MHz, CDCl_3



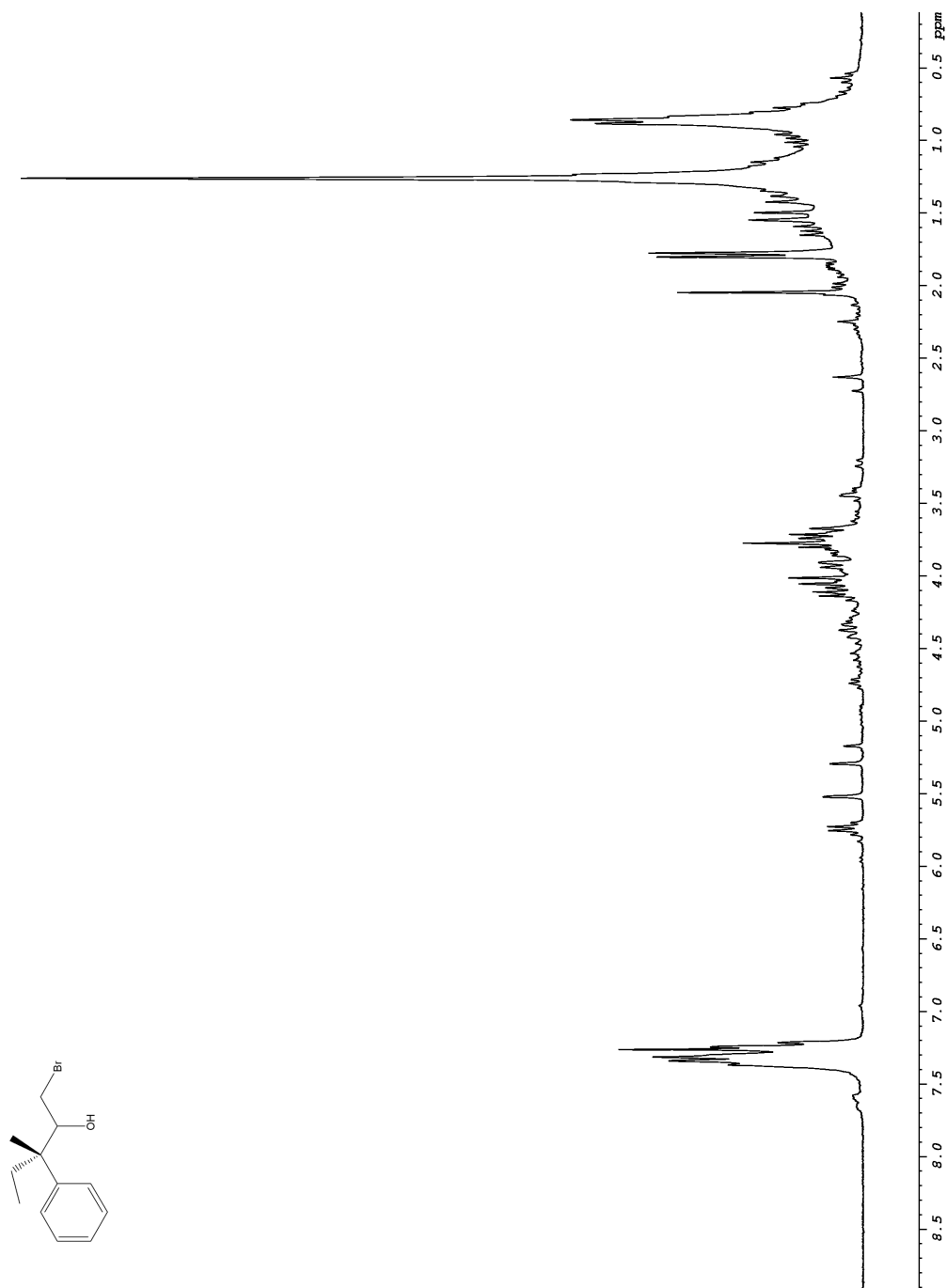
Bromohydrin **13** ^1H NMR, 250 MHz, CDCl_3
Product Mixture, Top Spot from Preparatory TLC Plate



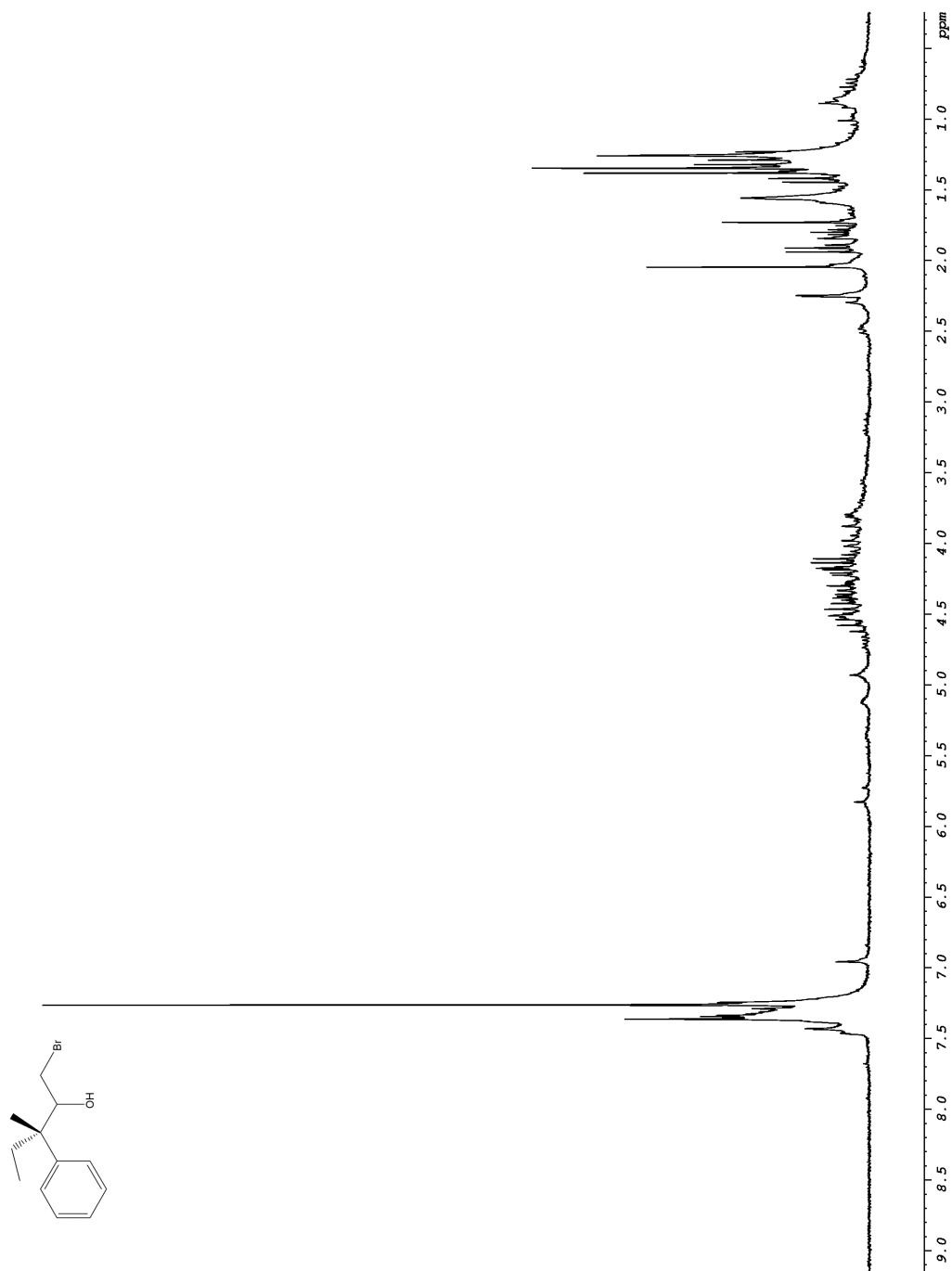
Bromohydrin **13** ^1H NMR, 250 MHz, CDCl_3
Product Mixture, Bottom Spot from Preparatory TLC Plate



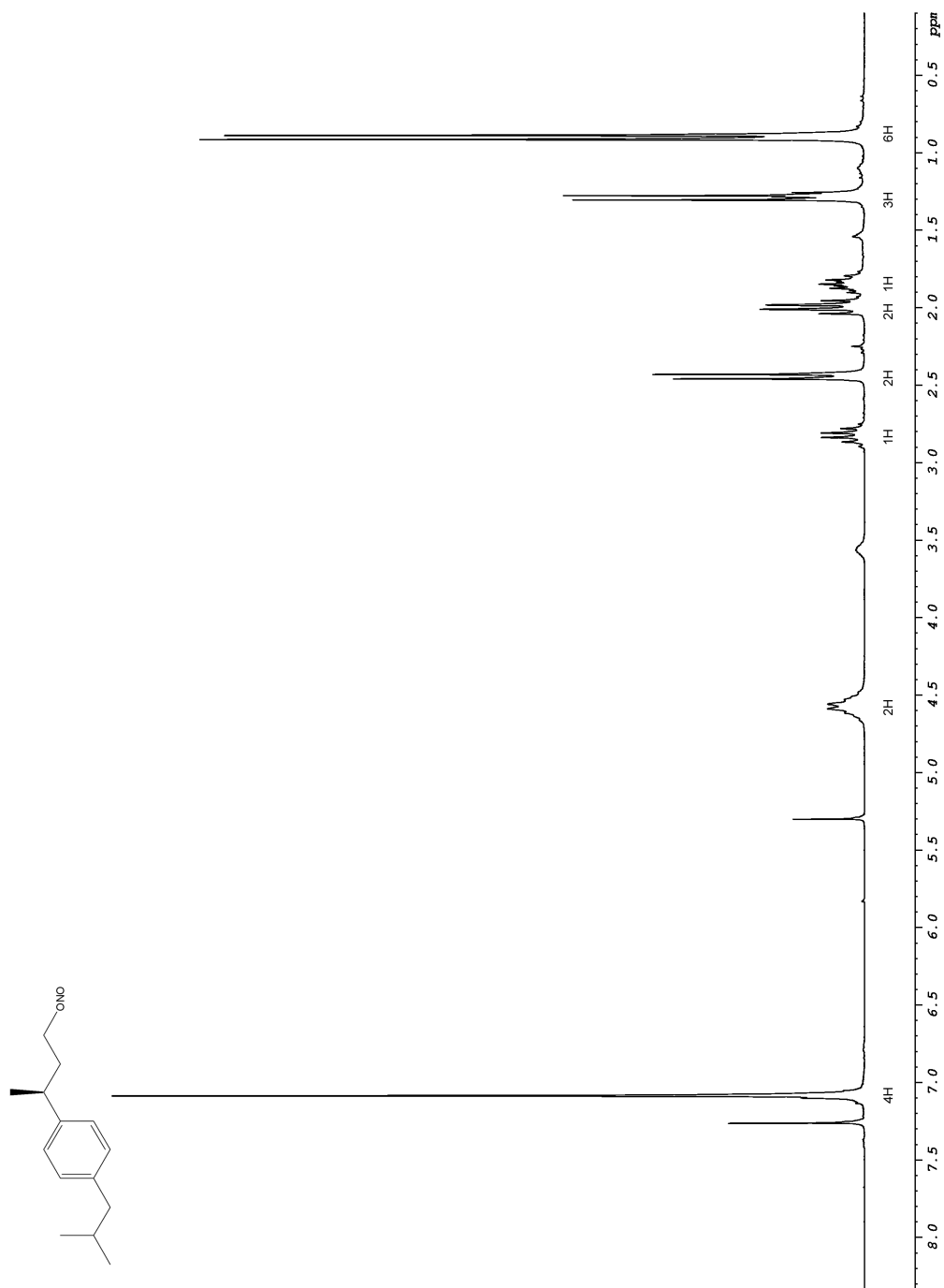
Bromohydrin **14** ^1H NMR, 250 MHz, CDCl_3
Product Mixture, Top Spot from Preparatory TLC Plate



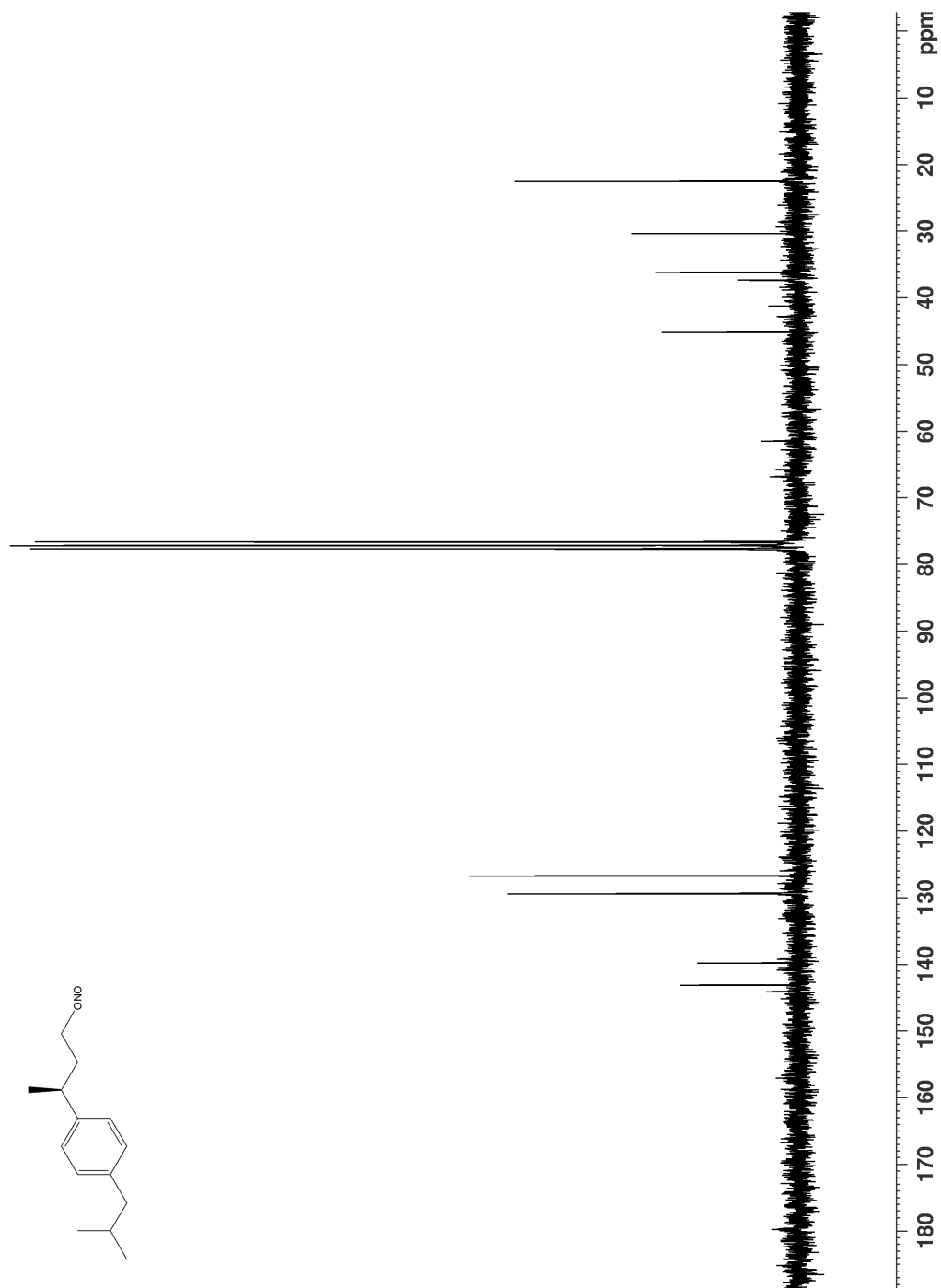
Bromohydrin **14** ^1H NMR, 250 MHz, CDCl_3
Product Mixture, Bottom Spot from Preparatory TLC Plate



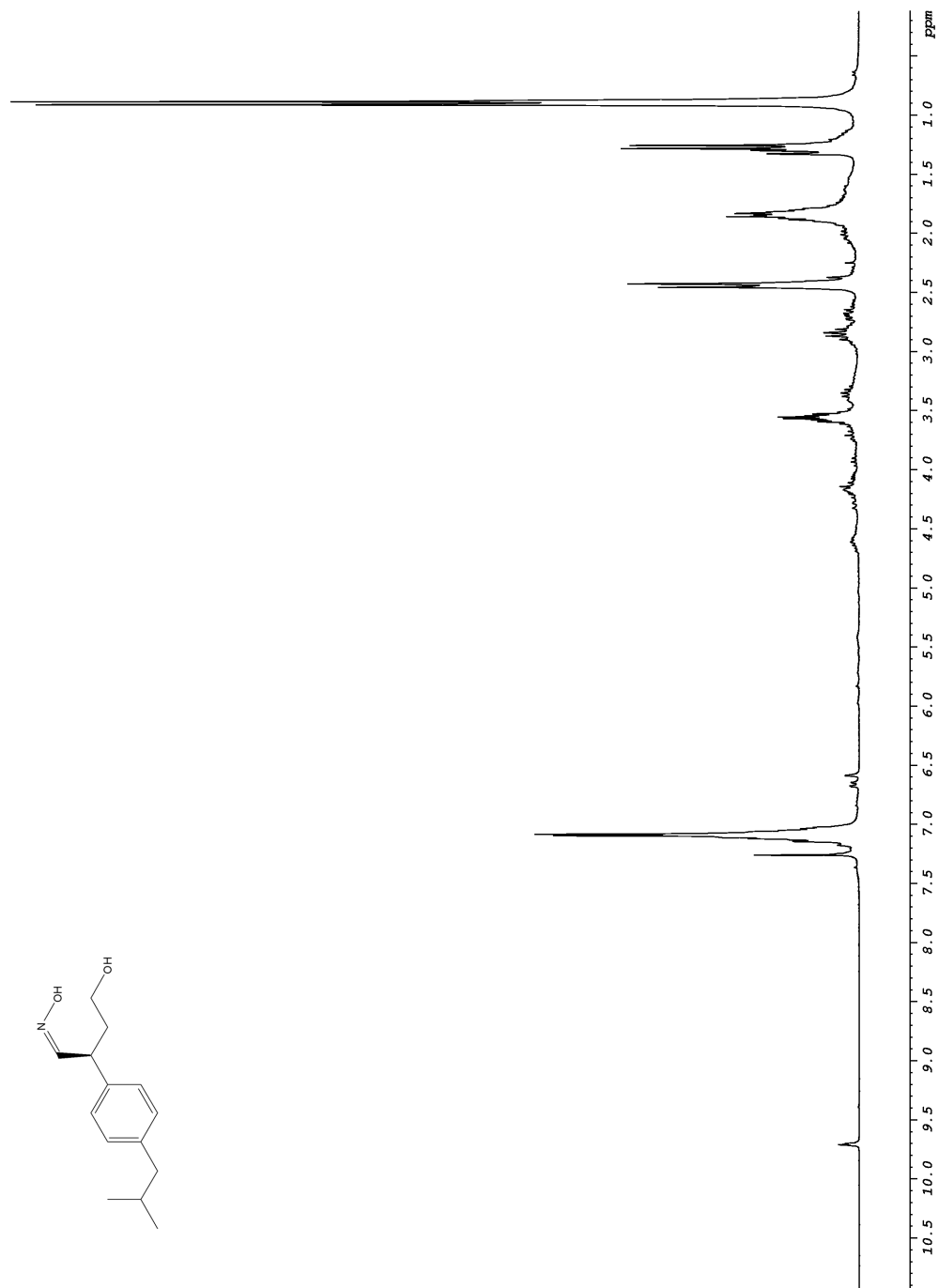
Nitrite **15** ^1H NMR, 250 MHz, CDCl_3



Nitrite **15** ^{13}C NMR, 62.9 MHz, CDCl_3



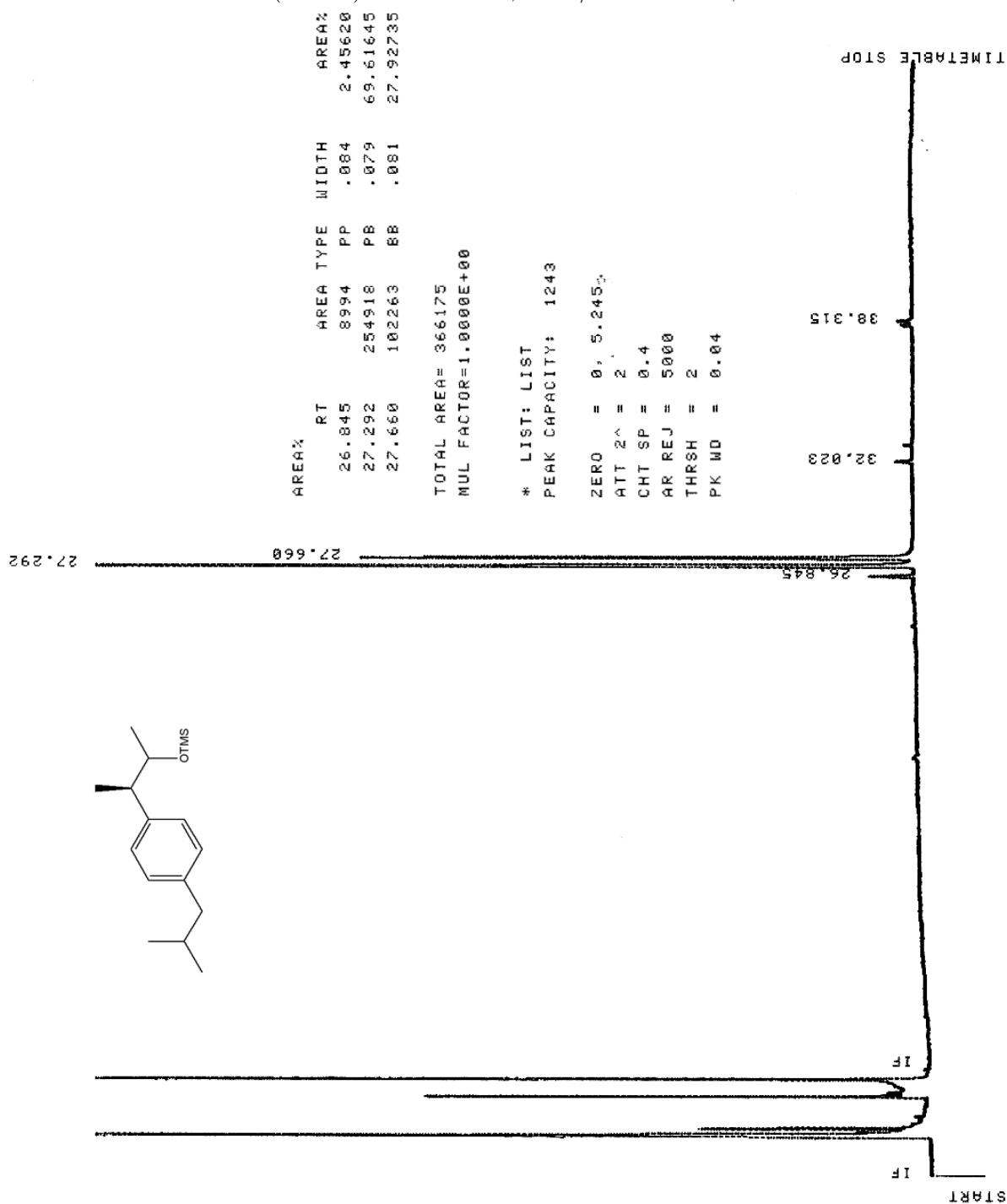
Crude Oxime **16** ^1H NMR, 250 MHz, CDCl_3



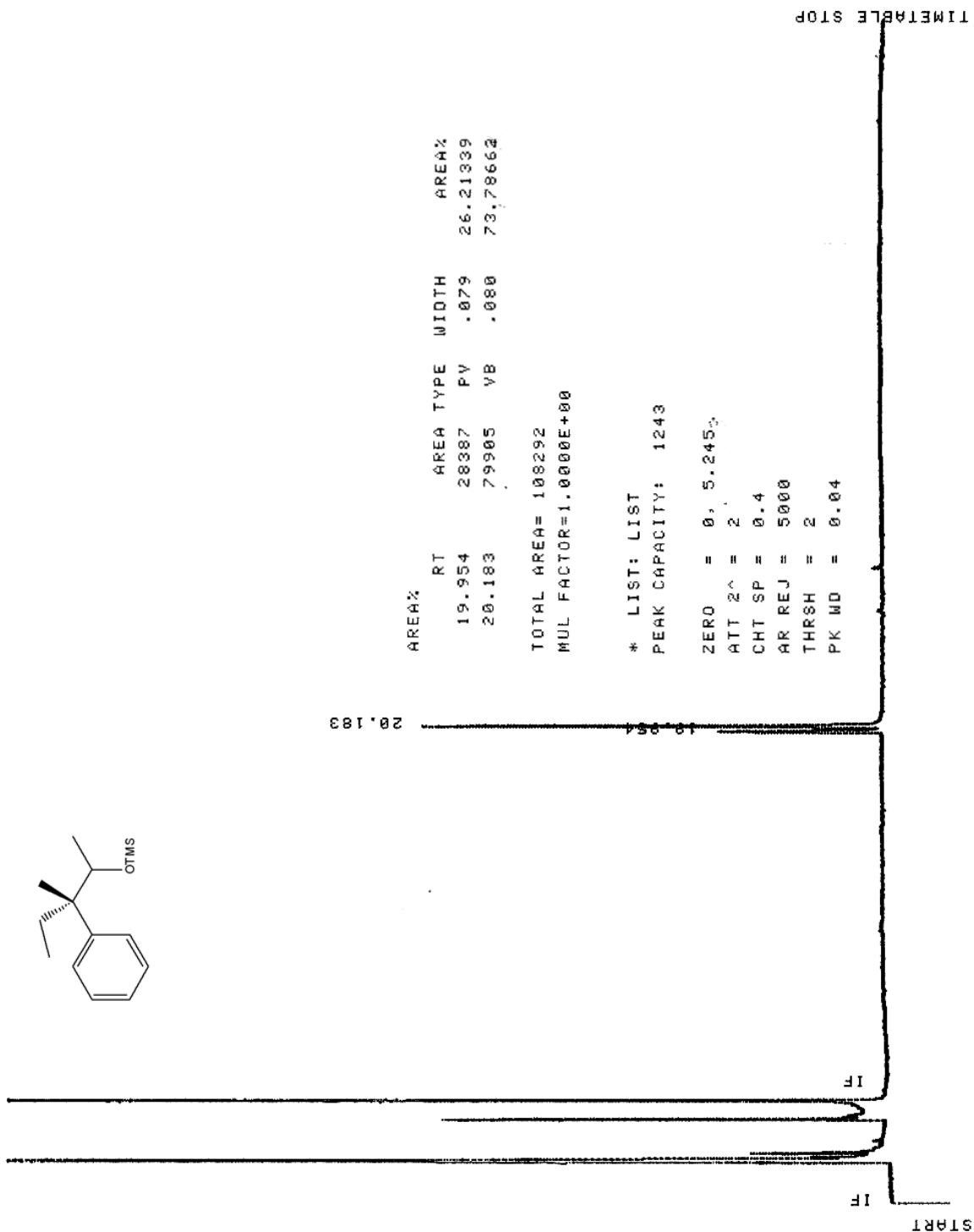
6.2 Appendix B, Gas Chromatography Traces

Alcohol 11, %de 42.7

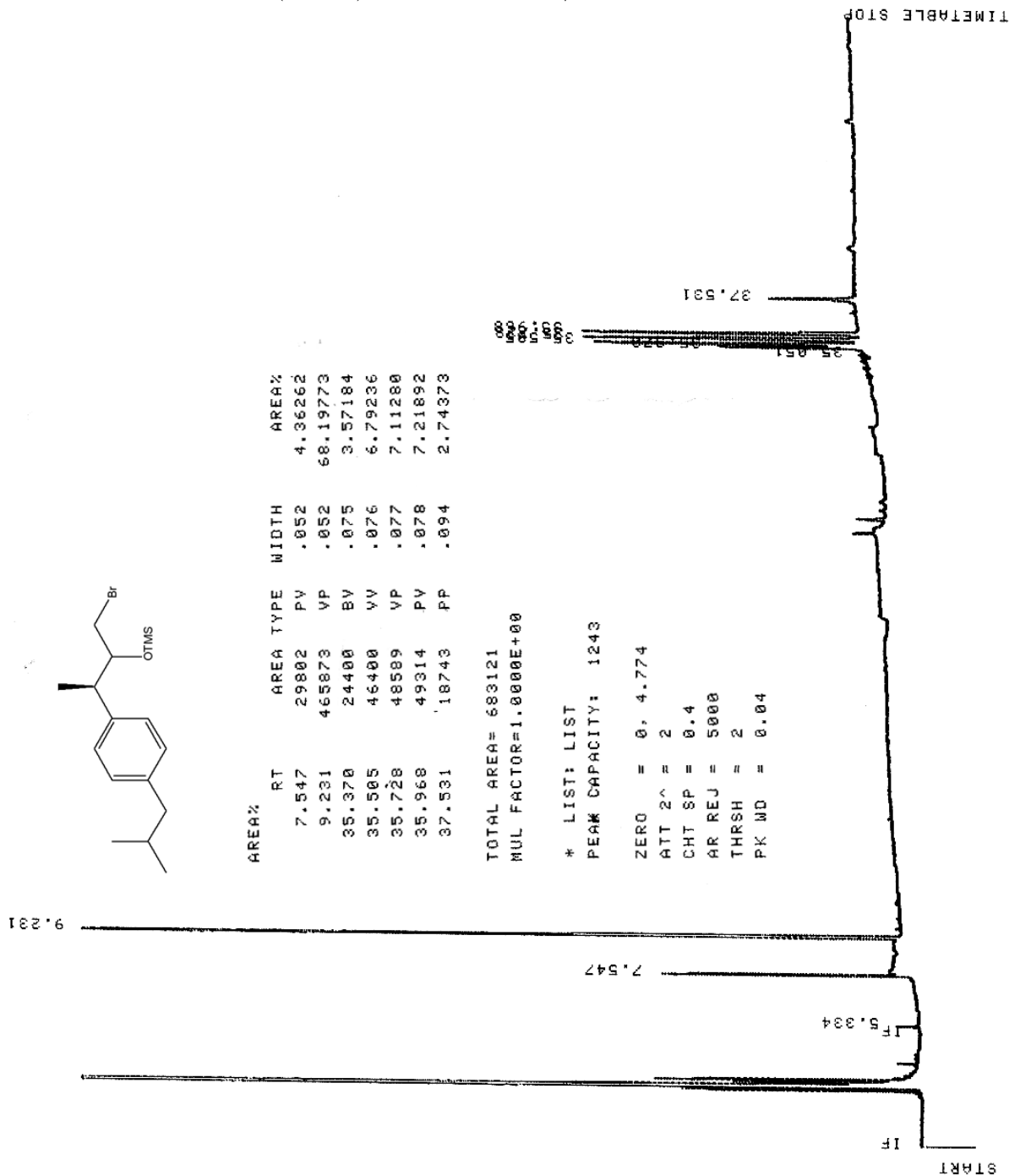
Conditions (achiral): 100°C 5 min, 2.5°C/min to 200°C, 200°C 5min



Alcohol **12**, %de 47.6
 Conditions (achiral): 100°C 5 min, 2.5°C/min to 200°C, 200°C 5min



Bromohydrin **13**, Major Product Mixture
 Conditions (achiral): 100°C 5 min, 5°C/min to 250°C, 250°C 15min



AREA%	RT	AREA	TYPE	WIDTH	AREA%
7.547	29802	PV	.052	4.36262	
9.231	465873	VP	.052	68.19773	
35.370	24400	BV	.075	3.57184	
35.505	46400	VV	.076	6.79236	
35.728	48589	VP	.077	7.11280	
35.968	49314	PV	.078	7.21892	
37.531	18743	PP	.094	2.74373	

TOTAL AREA= 683121

MUL FACTOR=1.0000E+00

* LIST: LIST

PEAK CAPACITY: 1243

ZERO = 0, 4.774

ATT 2^ = 2

CHT SP = 0.4

AR REJ = 5000

THRESH = 2

PK WD = 0.04